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ORIGINAL ARTICLE

Lower urinary tract symptoms as an independent predictor of aortic regurgitation in women with cardiac symptoms

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Abstract

Background: Very few studies have focused on the correlation between structural heart disease and lower urinary tract symptoms. In this study, we applied echocardiography to explore the correlation between lower urinary tract symptoms and structural heart disease.

Methods: In this single-center, prospective, cross-sectional study, we enrolled adult women undergoing echocardiography for suspected cardiac abnormalities causing cardiac symptoms between February 1, 2021, and March 31, 2021. All participants completed a questionnaire regarding demographic information and lower urinary tract symptoms, which were assessed according to the International Prostate Symptom Score.

Results: A total of 165 women aged 69.96 ± 10.20 years were enrolled. The prevalence of moderate-to-severe aortic regurgitation in patients with moderate-to-severe lower urinary tract symptoms was significantly higher than that in patients with mild lower urinary tract symptoms (33.3% vs 13.6%, $p = 0.008$). The prevalence of other echocardiographic abnormalities was not associated with severity of lower urinary tract symptoms. Multivariable logistic regression analyses revealed that moderate-to-severe lower urinary tract symptoms predicted moderate-to-severe aortic regurgitation ($p = 0.007$; odds ratio: 3.560; 95% confidence interval: 1.409-8.993). Furthermore, the International Prostate Symptom Score storage subscore ($p = 0.001$; odds ratio: 1.285; 95% confidence interval: 1.111–1.486), except the voiding subscore, was an independent predictor of moderate-to-severe aortic regurgitation.

Conclusion: Moderate-to-severe lower urinary tract symptoms, especially storage symptoms, are an independent predictor of the co-existence of moderate-to-severe aortic regurgitation in women with cardiac symptoms. Early cardiological referral of patients with moderate-to-severe lower urinary tract symptoms and cardiac symptoms may improve their general health.

Keywords: Aortic regurgitation; Echocardiography; Lower urinary tract symptoms

1. INTRODUCTION

Lower urinary tract symptoms (LUTS) are highly prevalent in both men and women and tend to increase with age. Liu et al investigated the prevalence of LUTS in 2068 adults with a mean age of 55 years in Taiwan.[1] According to the International Prostate Symptom Score (IPSS), 85% of individuals had at least mild LUTS (total score 1-7), and 30% had at least moderate symptoms (total score 8-19). Total percentages of individuals with or without IPSS symptoms were similar in both sexes. The prevalence of LUTS increased with age, and LUTS were more prevalent among individuals with a range of comorbidities, including diabetes, cardiac disease, and hyperlipidemia.

Cardiovascular disease is known as the leading cause of global death and one of the most serious health problems throughout the world.[2] Cardiovascular disease is responsible for a remarkable reduction in quality of life and life expectancy and also imposes huge costs on health systems in different countries.[3] Given its association with aging and the projected growth of the aging population, prevention of cardiovascular disease is a critical concern.[4]

The relationship between LUTS and cardiovascular disease has been extensively studied. Cardiovascular disease has been proposed as a potential risk factor for the progression and severity of LUTS. Furthermore, moderate-to-severe LUTS may be a sentinel marker for major adverse cardiac events.[5] The relationship between cardiovascular disease and LUTS may be attributed to several factors, including metabolic syndrome, chronic inflammation,

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atherosclerosis-induced pelvic ischemia, increased Rho-kinase activation, impaired nitric oxide synthase pathway in the endothelium, autonomic hyperactivity with sympathetic dysregulation, and declining testosterone levels.[6] The components of metabolic syndrome play a key role in the common pathophysiology of LUTS and cardiovascular disease.[7] Metabolic syndrome may cause alterations in vascular supply and innervation of the bladder and prostate; it is also associated with a larger total and transitional prostatic volume, which may result in the development of LUTS.[7]

Nevertheless, very few studies have focused on the correlation between structural heart disease and LUTS. Structural heart disease occurs when there is an abnormality or defect in the structure of one of the components of the heart, including the valves, chambers, muscles, walls that divide chambers from one another, or major arteries that transport blood from the heart to the lungs and body.[8] Mekki et al reported that nocturia, one of the LUTS, was independently predictive of electrocardiographic evidence of left ventricular hypertrophy and left atrial enlargement.[9] However, the mainstay of the evaluation of structural heart disease is not electrocardiography but echocardiography. Moreover, the relationship between structural heart disease and LUTS other than nocturia remains unclear. Therefore, the present study aimed at applying echocardiography to investigate the association between LUTS and structural heart disease.

2. METHODS

2.1. Ethical approval

The protocol for this research project has been approved by the ethics committee of our hospital (approval number: TCHIRB-11002002), and it conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from all study participants.

2.2. Study design and population

This single-center, prospective, cross-sectional study aimed to determine whether a correlation exists between LUTS and echocardiographic abnormalities. Because the presence of variable benign prostatic enlargement would be a significant confounding factor of LUTS, we focused on female patients only. This study included adult women undergoing echocardiography between February 1, 2021, and March 31, 2021, for suspected cardiac abnormalities causing symptoms such as chest pain or tightness. Patients with urinary tract infection, neurogenic bladder, a history of lower urinary tract or pelvic surgery, or a history of heart failure and cardiomyopathy were excluded. All participants completed a questionnaire on demographic information and LUTS.

2.3. Questionnaires

The questionnaire was composed of two parts. The first part collected data on demographic information, including age, body mass index (BMI), and comorbidities such as hypertension, diuretic use, and diabetes mellitus. The BMI was calculated using the formula: weight (in kg)/height squared (m^2). As per the Asia-Pacific cutoff points, BMI ≥ 25 kg/m^2 is considered obese.[10] The second part used the International Prostate Symptom Score (IPSS) for assessment of LUTS.

The IPSS consists of seven questions regarding voiding and storage symptoms. Each question is rated from 0 (not at all) to 5 (almost always). The severity of LUTS, based on the total score, was classified as mild (0-7), moderate (8-19), or severe (20-35).

2.4. Echocardiography

Transthoracic echocardiography was conducted and analyzed by the same echocardiographer and validated by a cardiologist specializing in echocardiography. The cardiologist was blinded to the IPSS results. Doppler echocardiography was performed, and measurements were obtained by following a standard protocol according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[11] The recommendations considered were as follows:

1. Size and thickness of the left ventricle.
2. Diameter of the left atrium.
3. Diameters of the aortic root.
4. Ejection fraction of the left ventricle.
5. Diastolic function of the left ventricle.
6. Evaluation of the mitral, aortic, tricuspid, and pulmonary valvular systems. Valvular heart disease was diagnosed and rated using an integrative approach as recommended by the European Association of Echocardiography.[12,13]
7. Regurgitant velocity of the tricuspid valve.

2.5. Statistics

Descriptive statistical analysis was performed based on two subgroups represented by mild and moderate-to-severe LUTS (defined as IPSS ≥ 8). The chi-square test was used to test the relationships between categorical variables. Multivariable logistic regression analyses, adjusted for demographic covariates and comorbidities, were performed to determine whether moderate-to-severe LUTS was predictive of echocardiographic abnormalities. For statistical analyses, we used the software package IBM SPSS Statistics for Mac, version 24.0 (IBM Corporation, Armonk, NY, USA). A p-value of <0.05 is reported as statistically significant.

3. RESULTS

A total of 165 women were enrolled, with a mean ± standard deviation age of 69.96 ± 10.20 years. The demographic characteristics and echocardiographic results of all participants are summarized in Table 1. Among the participants, seventeen patients reported no LUTS and 148 (89.7%) had at least one LUTS. Furthermore, 80% (132/165) had mild LUTS (IPSS total score 0-7), and 20% (33/165) had moderate-to-severe LUTS (IPSS total score ≥ 8). The prevalence of moderate-to-severe aortic regurgitation (MSAR) in patients with moderate-to-severe LUTS was significantly higher than that in the mild LUTS group (33.3% vs 13.6%, p = 0.008). Other variables were not significantly different between patients with moderate-to-severe LUTS and those with mild LUTS.

Multivariable logistic regression analyses, adjusted for all demographic covariates and comorbidities, were performed to determine whether moderate-to-severe LUTS was predictive of echocardiographic abnormalities. As a result, only MSAR (p = 0.007; odds ratio [OR]: 3.560; 95% confidence interval [CI]: 1.409-8.993) was predicted by moderate-to-severe LUTS. Furthermore, we explored the associations between IPSS subscores and MSAR (Table 2). The IPSS storage subscore (p = 0.001; OR: 1.285; 95% CI: 1.111–1.486) was an independent predictor of MSAR. However, no significant association was observed between IPSS voiding subscore and MSAR (p = 0.102; OR: 1.088; 95% CI: 0.983-1.204). Additionally, diabetes mellitus was associated with a borderline significant decrease in the risk of MSAR (p = 0.043; OR: 0.262; 95% CI: 0.072-0.956) in model III, which explored the association between the IPSS storage subscore and MSAR.

4. DISCUSSION

To the best of our knowledge, the current study is the first to determine the correlation between LUTS and echocardiographic abnormalities in women. We observed that moderate-to-severe

Table 1

Demographic description and echocardiographic results of the study participants

	Total (n = 165)	Mild LUTS (n = 132)	Moderate-to-severe LUTS (n = 33)	*p*
Age, y old				0.79
<65, N (%)	43 (26.1)	35 (26.5)	8 (24.2)	
≥65, N (%)	122 (73.9)	97 (73.5)	25 (75.8)	
BMI				0.815
<25, N (%)	87 (52.7)	69 (52.3)	18 (54.5)	
≥25, N (%)	78 (47.3)	63 (47.7)	15 (45.5)	
HTN				0.218
No, N (%)	44 (26.7)	38 (28.8)	6 (18.2)	
Yes, N (%)	121 (73.3)	94 (71.2)	27 (81.8)	
Diuretics use				0.199
No, N (%)	157 (95.2)	127 (96.2)	30 (90.9)	
Yes, N (%)	8 (4.8)	5 (3.8)	3 (9.1)	
DM				0.143
No, N (%)	126 (76.4)	104 (78.8)	22 (66.6)	
Yes, N (%)	39 (23.6)	28 (21.2)	11 (33.3)	
Aortic dilatation				0.49
No, N (%)	162 (98.2)	130 (98.5)	32 (97.0)	
Yes, N (%)	3 (1.8)	2 (1.5)	1 (3.0)	
LAE				0.613
No, N (%)	114 (69.1)	90 (68.2)	24 (72.7)	
Yes, N (%)	51 (30.9)	42 (31.8)	9 (27.3)	
LVH				1
No, N (%)	120 (72.7)	96 (72.7)	24 (72.7)	
Yes, N (%)	45 (27.3)	36 (27.3)	9 (27.3)	
Concentric remodeling				0.431
No, N (%)	95 (57.6)	78 (59.1)	17 (51.5)	
Yes, N (%)	70 (42.4)	54 (40.9)	16 (48.5)	
AR				0.008
Absent to mild, N (%)	136 (82.4)	114 (86.4)	22 (66.7)	
Moderate to severe, N (%)	29 (17.6)	18 (13.6)	11 (33.3)	
TR				0.336
Absent to mild, N (%)	102 (61.8)	84 (63.6)	18 (54.5)	
Moderate to severe, N (%)	63 (38.2)	48 (36.4)	15 (45.5)	
MR				0.448
Absent to mild, N (%)	114 (69.1)	93 (70.5)	21 (63.6)	
Moderate to severe, N (%)	51 (30.9)	39 (29.5)	12 (36.4)	
PR				0.496
Absent to mild, N (%)	132 (80.0)	107 (81.1)	25 (75.8)	
Moderate to severe, N (%)	33 (20.0)	25 (18.9)	8 (24.2)	
All values given as number (%)				

AR = aortic regurgitation; BMI = body mass index; DM = diabetes mellitus; HTN = hypertension; LUTS = lower urinary tract symptoms; LAE = left atrial enlargement; LVH = left ventricular hypertrophy; MR = mitral regurgitation; PR = pulmonary regurgitation; TR = tricuspid regurgitation.

LUTS was an independent predictor of MSAR, and that the higher storage subscore of IPSS independently predicted MSAR. However, the IPSS voiding subscore was not a significant independent predictor of MSAR. Additionally, diabetes mellitus was associated with a borderline significant decrease in the risk of MSAR.

Hemodynamic forces are possible contributory factors in aortic atherosclerosis. Aortic regurgitation (AR) causes increased stroke volume, high pulse pressure, and diastolic retrograde flow that extends to the distal aorta. Zhou et al showed that AR changes the distribution of atherosclerotic lesions and reinforces atherogenesis in a mouse model.[14] Shimoni et al reported that the prevalence of descending aortic atherosclerosis increased in patients with significant AR.[15] Many animal studies have suggested that arterial occlusive diseases such as atherosclerosis may lead to lower urinary tract dysfunction through bladder ischemia, hypoxia, and oxidative stress in the bladder.[16–19] Clinical studies have also shown that LUTS and lower urinary tract dysfunction occur if underlying diseases lead to atherosclerotic changes in the bladder. This interferes with the blood flow to the bladder.[20–24] Consequently, AR may cause LUTS via aortic atherosclerosis-induced bladder ischemia.

Bladder ischemia causes oxidative stress, which is characterized by the upregulation of oxidative stress-sensitive genes, increased muscarinic receptor activity, ultrastructural damage, and neurodegeneration.[25] Rabbit models have shown that moderate ischemia leads to bladder overactivity, whereas severe ischemia leads to bladder underactivity.[16,26] In a rat model with chronic bladder ischemia, micturition interval, bladder capacity, and voided volume were significantly lower than the respective values in the control group.[19] As a result, bladder ischemia caused by MSAR may play a crucial role in the pathophysiology of bladder dysfunctions, such as detrusor overactivity, which is manifested in the present study as increased storage symptoms.

Singh et al conducted a prospective large-scale epidemiologic study (the Framingham Heart Study) and reported that the prevalence and severity of AR increased with age; when classified by decade of life, MSAR was identified in <1% of participants

Table 2

Multivariable logistic regression analyses of variables associated with moderate to severe aortic regurgitation among participants

	Model I		Model II		Model III	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age, y						
<65	1		1		1	
≧65	1.574 (0.558-4.435)	0.391	1.552 (0.556-4.333)	0.401	1.414 (0.493-4.055)	0.519
BMI						
<25	1		1		1	
≧25	0.872 (0.356-2.139)	0.765	0.864 (0.358-2.083)	0.744	0.949 (0.377-2.389)	0.911
HTN						
No	1		1		1	
Yes	0.673 (0.244-1.856)	0.444	0.703 (0.262-1.889)	0.485	0.725 (0.255-2.066)	0.547
Diuretics use						
No	1		1		1	
Yes	2.578 (0.512-12.991)	0.251	3.310 (0.693-15.809)	0.133	2.174 (0.407-11.624)	0.364
DM						
No	1		1		1	
Yes	0.375 (0.114-1.232)	0.106	0.476 (0.150-1.512)	0.208	0.262 (0.072-0.956)	0.043
IPSS grade						
Mild	1					
Moderate to severe	3.560 (1.409-8.993)	0.007				
IPSS-V			1.088 (0.983-1.204)	0.102		
IPSS-S					1.285 (1.111-1.486)	0.001

BMI = body mass index; DM = diabetes mellitus; HTN = hypertension; IPSS = International Prostate Symptom Score; IPSS-V = IPSS voiding subscore; IPSS-S = IPSS storage subscore.

in all subgroups aged <70 years.[27] In the present study, age was not significantly associated with MSAR. We attribute the difference between the Framingham Study and our study to older participants with suspected cardiac abnormalities and the focus on MSAR in our study.

In the present study, obesity (BMI ≥ 25 kg/m^2) was not shown to be a risk factor for AR. Our findings are supported by those of Lebowitz et al,[28] who showed no difference in the prevalence of AR between obese and nonobese participants.[28] In addition, the Framingham Study reported no significant correlation between BMI and AR.[27] Furthermore, Julius et al reported that BMI was not significantly correlated with the presence of AR in obese participants.[29]

Although previous studies reported that hypertension tended to lead to aortic root enlargement and subsequent AR, later pathological and M-mode echocardiographic studies have not demonstrated a correlation between hypertension and aortic enlargement when considering age.[30,31] The Framingham Study has shown that the presence of hypertension is unrelated to AR.[27] Our results support those of the Framingham Study, demonstrating the lack of association between hypertension and MSAR. Comparatively, a recent study on 5.4 million adults in the UK (median age, 39 years) without known cardiovascular disease or aortic valve disease at baseline reported that above a systolic blood pressure of 115 mmHg, every additional 20 mmHg was correlated with a 38% higher risk of AR later in life, with stronger correlations identified in younger groups.[32] The study design (cross-sectional vs longitudinal) and age (69.96 ± 10.20 years) of participants with suspected cardiac abnormalities in the present study may be responsible for the differences between our study and the UK study.

Our study found that diabetes mellitus was associated with a significant decrease in the risk of MSAR, which implies a protective role of diabetes mellitus in the development of AR. Similarly, Lebowitz et al demonstrated that the absence of diabetes mellitus was associated with AR.[28] A previous study has described the essential role of the aortic root in supporting the aortic valve cusps, such that dilation of the root may reduce the overlap between leaflets and thereby promote regurgitation.[28] Compared with other arteries, the aorta experiences considerably greater wall stress, and aortic dilation is a typical aging process.[33] Patients with diabetes have been shown to have a larger matrix volume and increased aortic wall thickness, which decreases aortic wall stress.[34,35] Recent studies have indicated that hyperglycemia associated with diabetes mellitus plays a crucial role in stabilizing the collagen network via crosslinking of collagen in the aortic wall media.[34,35] The aforementioned studies have provided evidence for the protective effect of diabetes mellitus on the development of AR.

Our study has several limitations. First, a cross-sectional design was used to analyze the association between LUTS and structural heart disease, which may limit conclusions regarding the causal relationship. Consequently, a longitudinal study is required to explore the direction of the correlation. Second, the study focused on women undergoing echocardiography for suspected cardiac abnormalities, which may limit the generalizability of the results. Third, the present study did not consider risk factors that could affect LUTS severity in women, such as chronic constipation, or parity. Fourth, we did not use a multichannel urodynamic study to evaluate lower urinary tract dysfunction, and the pathophysiology of lower urinary tract dysfunction could not be definitively identified.

In conclusion, moderate-to-severe LUTS, especially storage symptoms, were an independent predictor of the co-existence of MSAR in women with cardiac symptoms. We suggest that this relationship should be kept in mind when evaluating patients with moderate-to-severe LUTS. Early referral of such patients to a cardiologist may be helpful to improve their general health.

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