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Coronary Artery Disease

Relationship between the Severity of Coronary Artery Disease and Overactive Bladder

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Background: Overactive bladder is a urological disease that can seriously impair a person's quality of life, however its etiology remains unclear. The aim of this study was to evaluate the relationship between overactive bladder and SYNTAX score, which is based on coronary angiographic imaging to evaluate the severity of coronary artery disease.
Methods: A total of 380 patients diagnosed with coronary artery disease by coronary angiography were included in the study. Each participant completed the Overactive Bladder-Validated 8 questionnaire. The patients were divided into two groups as overactive bladder (n = 177; score ≥ 8), and non-overactive bladder (n = 203; score < 8). SYNTAX scores were calculated for both groups and compared.
Results: The SYNTAX score was significantly higher in the patients with overactive bladder (25.4 ± 4.2) than in those without an overactive bladder (18.3 ± 3.4) ($p < 0.001$). In addition, age, smoking rate, body mass index and diabetes mellitus were significantly higher and heart rate was significantly lower in the overactive bladder group ($p < 0.001$). In logistic regression analysis, the SYNTAX score was the sole independent predictor of overactive bladder (odds ratio: 1.47, 95% confidence interval: 1.35-9.19, $p < 0.001$).
Conclusions: Our study suggests that the presence of a high SYNTAX score in patients with coronary artery disease may be associated with overactive bladder.

Key Words: Coronary artery disease • Overactive bladder • Pelvic ischemia

INTRODUCTION

Atherosclerosis is a chronic inflammatory disease in which systemic arteries are affected from the aorta to epicardial coronary arteries.[1] Atherosclerosis is the most common underlying cause of coronary artery disease (CAD), carotid artery disease, and peripheral artery disease.[2] Atherosclerotic patients are asymptomatic for many years, and symptomatic presentations are mostly in the form of an acute coronary event.[3] When atherosclerosis affects the coronary arteries as a systemic disease, various other arteries in the body can also be affected.[4] Therefore, if an arterial bed is detected to be affected by obstructive atherosclerotic disease, other arterial beds should also be examined.

Overactive bladder (OAB) is associated with troubling symptoms such as a sudden and frequent urge to void and nocturia, and thus seriously impairs a person's quality of life.[5] Although the etiology of OAB is not yet known clearly, many causes such as advanced age, central and peripheral neuropathy and atherosclerosis are proposed etiologies.[6] Oxidative stress due to hypoxia has been shown to increase collagen content in the bladder wall and impair the neurogenic functionality of the bladder.[7,8] Restriction of the pelvic blood supply, atherosclerosis, and endothelial dysfunction have also been implicated in the formation of this pathology.[9] On the other hand, it has been shown that pelvic ischemia that develops with a background of atherosclerosis can lead to de-

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trusor overactivity.[10] In animal experiments, rabbits with chronic bladder ischemia have been shown to have detrusor overactivity in cytometry.[11] Previous studies have also demonstrated a relationship between OAB and atherosclerotic burden.

The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) is a coronary angiography-based scoring system used to rate the anatomical and atherosclerotic severity of CAD.[12] In the current study, we hypothesized that OAB may develop as a result of both atherosclerotic burden and CAD. To test this hypothesis, we investigated the relationship between CAD and SYNTAX score, which is an indicator of coronary plaque burden, severity, mortality and morbidity due to CAD.

METHODS

Patients

The study was conducted following the ethical guidelines of the Declaration of Helsinki. A total of 380 patients who underwent coronary angiography between March 2019 and May 2020 were examined after obtaining the approval of the local ethics committee and patient consent. Patients indicated for coronary angiography were initially questioned for a detailed medical history, including chronic diseases, previous surgery, medications used, and smoking status (active smokers or ex-smokers who had stopped smoking for < 3 months). Body mass index (BMI) was calculated by dividing the body weight by the square of body height. Blood and urine samples were taken for the analysis of serum glucose, cholesterol panel, hemogram, blood urea nitrogen, creatinine, complete urinalysis, and urine culture. All serum samples were taken after 12 hours of fasting. Each patient was subjected to a uroflowmetry test, and their post-void residual urine volume was measured. To obtain a homogeneous group, patients with chronic diseases, such as uncontrolled diabetes mellitus (HbA1c > 7), heart failure, neurological diseases, neurogenic bladder, renal failure, urinary tract infection, nephrolithiasis and a history of pelvic surgery or radiotherapy, those who had been previously diagnosed with benign prostatic hyperplasia or bladder or prostate cancer, and those receiving antimuscarinic agents and mirabegron for OAB, or using diuretics or alpha blockers were excluded from the study. Therefore, all underlying pathological and metabolic conditions that could cause OAB were excluded. Patients with a maximum flow rate of < 15 ml/s in uroflowmetry and those with a post-void residual urine volume of > 100 cc were also excluded (Figure 1).

The SYNTAX scores of all patients included in the study were calculated by obtaining the sum of the score of each lesion. SYNTAX scores were calculated by two experienced interventional cardiologists who were blinded to the subjects' clinical status, including Overactive Bladder-Validated 8 (OAB-V8) questionnaire scores. All participants completed the OAB-V8 questionnaire before the coronary procedures. This scoring system is aimed at questioning patients' void-related symptoms, including urgency, frequency, nocturia, and urgency urinary incontinence. In the OAB-V8 scoring system, it is commonly accepted that OAB is present if the score is ≥ 8, and that OAB is controversial or absent if the score is < 8.[13] Accordingly, we divided our patients into two groups according to the severity of OAB: OAB group (those with a score of ≥ 8), and non-OAB group (those with a score of < 8).

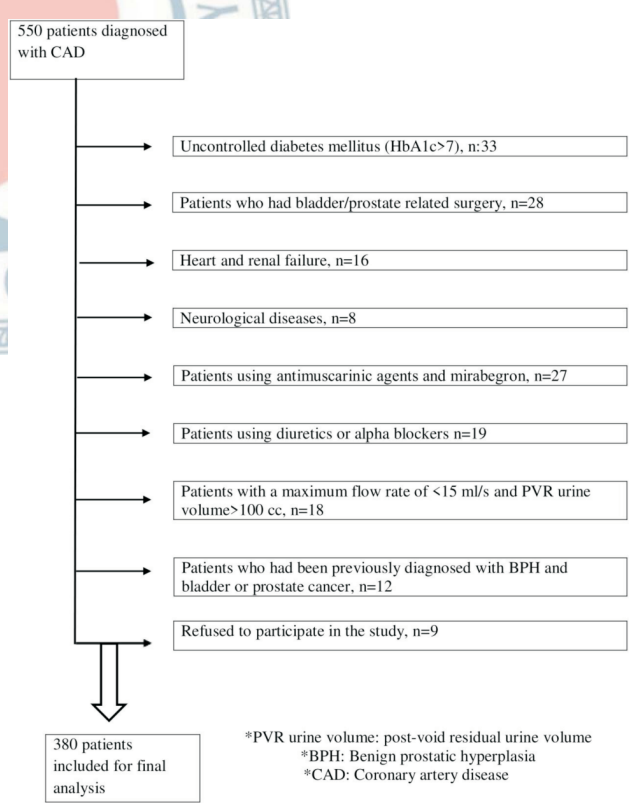

Figure 1. *Flowchart of the patients in the study.*

Angiographic evaluation and calculation of the SYNTAX score

Coronary angiography was performed through the radial or femoral arteries using standard techniques in the angiography laboratory of Ataturk University Research Hospital, Department of Cardiology. Coronary angiography and percutaneous coronary interventions (PCIs) were performed by three experienced interventional cardiology specialists. The left anterior descending artery and left circumflex artery were evaluated in at least four views, and the right coronary artery in at least two views. Calibration was performed with reference to the computer support diagnostic catheter diameter. Segments with a coronary artery lesion were marked from proximal to distal. Diameter and lumen stenosis were measured automatically. Non-ionic low-osmolar contrast agents were used during coronary angiography. Patients with coronary artery lesions causing more than 50% lumen diameter narrowing in arteries with a diameter of 1.5 mm or larger were included in the study. The total SYNTAX score was obtained by calculating the score of each lesion separately.[14] The SYNTAX score was determined using a coefficient determined by considering the morphological features of each lesion and software that calculated the scores of each lesion individually (SYNTAX score calculator v2.02, www.syntaxscore.com).

Since ST-elevation myocardial infarction (STEMI) is among the exclusion criteria in the SYNTAX study, there is no accepted SYNTAX score calculation method for these patients in the current score algorithm. An alternative scoring algorithm can therefore be considered to calculate the SYNTAX score in STEMI patients. Since STEMI is an acute event, when calculating the SYNTAX score for these patients, if the artery responsible for the infarct was totally occluded, it was scored as being "occluded for less than three months" and included in the algorithm, resulting in an additional five points being added to the total score.

Statistical analysis

SPSS for Windows, version 21.0 (IBM SPSS, Inc., Chicago, IL, USA) was used for all data analysis. Categorical variables were expressed as the number of cases and percentages, and the chi-square test was used in group comparisons. Continuous variables were presented as mean $\pm$ standard deviation. The Kolmogorov-Smirnov test was used to evaluate the normality assumption. The Student's t-test was used to compare variables with normal distribution, and the Mann-Whitney U test was used for non-normally distributed variables.

Three subgroups were classified according to the SYNTAX score (SYNTAX < 22, 23 < SYNTAX < 32; SYNTAX > 32), and differences in the OAB-V8 score between the three subgroups were compared using ANOVA followed by the Tukey post-hoc.

The Pearson or Spearman correlation test was conducted to determine the correlations between variables. Differences were considered significant at $p < 0.05$.

A multivariate logistic regression analysis model was used to evaluate the relationship of different variables with OAB. The ability of the model to discriminate patients with and without OAB was also analyzed based on receiver operating characteristic (ROC) curves.

RESULTS

A total of 550 patients diagnosed with CAD by coronary angiography were obtained by screening. Of these patients, 170 were excluded based on the predetermined criteria. Thus, 380 patients were evaluated and divided into two groups as OAB (OAB-V8 score ≥ 8, n = 177) and non-OAB (OAB-V8 score < 8, n = 203). The main characteristics of the patients are shown in Table 1. There were no significant differences between the two groups in terms of gender distribution, accompanying CAD risk factors, hypertension and dyslipidemia (all $p > 0.05$); however, age, BMI, diabetes mellitus, smoking rate, and heart rate significantly differed (all $p < 0.05$). The SYNTAX score was significantly higher in the OAB group than in the non-OAB group (25.4 ± 4.2 and 18.3 ± 3.4, respectively; $p < 0.001$). Analysis between SYNTAX score tertiles revealed statistically significant differences between the OAB-V8 score and SYNTAX score tertiles (Figure 2). Correlation analysis showed that SYNTAX score was significantly positively correlated with OAB-V8 score ($r = 0.672$, $p < 0.001$) (Table 2).

Variables showing significant correlations were further included in logistic regression analysis in order to test whether or not they might be independent risk factors for OAB. For this purpose, significant factors ob-

Table 1. Baseline characteristics of the patient groups

Parameters	Group 1 (with OAB) n = 177	Group 2 (without OAB) n = 203	p value
Age (years)	66.2 ± 10.2	58.5 ± 6.7	< 0.001
Gender			0.321
Male, n (%)	78 (44.1%)	98 (48.3%)	
Female, n (%)	99 (55.9%)	105 (51.7%)	
Diabetes mellitus, n (%)	98 (55.3%)	63 (31%)	0.003
Hypertension, n (%)	65 (36.7%)	68 (33.4%)	0.612
SBP (mmHg)	127.1 ± 8.3	126.3 ± 6.2	0.592
DBP (mmHg)	72.2 ± 5.6	73.1 ± 4.9	0.643
Dyslipidemia, n (%)	67 (37.8%)	87 (42.8%)	0.572
Smoker, n (%)	104 (58.7%)	68 (13.8%)	< 0.001
BMI (kg/m^2)	29.7 ± 3.6	23.6 ± 4.2	< 0.001
Heart rate, bpm	74 ± 15	83.4 ± 12	< 0.001
Hemoglobin, g/dL	13.4 ± 1.5	14.6 ± 3.2	0.238
Creatinine (mg/dL)	0.82 ± 0.13	0.77 ± 0.32	0.082
eGFR (mL/min/1.73 m^2)	77.2 ± 13.4	82.5 ± 12.5	0.921
Total cholesterol (mg/dl)	196 ± 35	174 ± 55	0.118
Triglyceride (mg/dl)	173 ± 96	144 ± 74	0.125
HDL-cholesterol (mg/dl)	39 ± 6	43 ± 5	0.152
LDL-cholesterol (mg/dl)	126 ± 37	108 ± 32	0.312
OAB-V8	21.21 ± 3.62	6.52 ± 2.94	< 0.001
SYNTAX score	25.4 ± 4.2	18.3 ± 3.4	< 0.001
Medications			
ASA n (%)	94 (53.1%)	105 (51.7%)	0.587
Clopidogrel	54 (30.5%)	61 (30.0%)	0.862
Ticagrelor	18 (10.1%)	26 (12.8%)	0.503
Prasugrel	21 (11.8%)	17 (8.3%)	0.397
ACE inhibitors/ARB, n (%)	60 (33.8%)	76 (37.4%)	0.428
β-blockers, n (%)	39 (22%)	57 (28%)	0.281
Calcium channel blockers	12 (6.7%)	13 (6.4%)	0.934
Statins, n (%)	45 (25.4%)	64 (31%)	0.354

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OAB, overactive bladder; OAB-V8, overactive bladder-validated 8; SBP, systolic blood pressure.

tained from the univariate analysis ($p < 0.02$) were included in the multivariate analysis (age, smoking status, BMI, heart rate, diabetes mellitus, and SYNTAX score). In the multivariate logistic regression analysis, SYNTAX score was identified as the sole independent predictor of OAB [odds ratio (OR): 1.07, 95% confidence interval (CI): 1.05-1.09; $p < 0.001$] (Table 3). ROC analysis revealed that a SYNTAX score of 21.3 was the cut-off point for OAB (area under the curve: 0.853) (Figure 3). A SYNTAX score > 21.3 predicted OAB at a sensitivity of 81.9% and specificity of 93.1% (positive predictive value: 91.1% and negative predictive value: 85.5%).

DISCUSSION

OAB is defined as a complex of troubling symptoms accompanied by a sudden and frequent urge to void and nocturia, presenting with or without urinary incontinence without any underlying organic pathology or urinary infection.[15] Although the main symptom is a sudden urge to void, urinary incontinence may or may not accompany this symptom. The incidence of OAB is different between genders, and although it is very variable, it has been reported to be 6.5-18% in men and 9.3-32.6% in women.[16] The incidence increases with

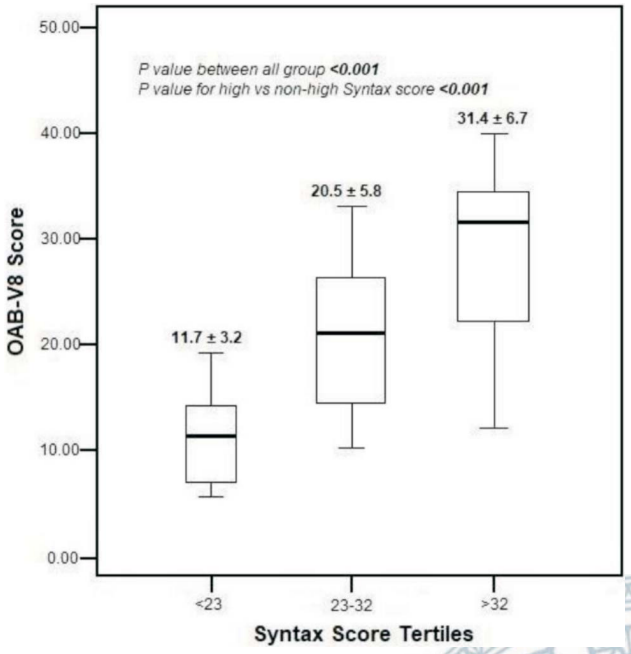

Figure 2. *OAB-V8 score values according to the Syntax score subgroups in patients with overactive bladder (OAB).*

Table 2. Correlation analysis of OAB-V8 with other parameters

Variables	r value	p value
Age (years)	0.493	0.004
Diabetes mellitus	0.346	0.013
Smoker	0.129	0.042
BMI (kg/m^2)	0.106	0.031
Heart rate (bpm)	-0.168	0.014
SYNTAX score	0.672	< 0.001

BMI, body mass index; OAB-V8, overactive bladder-validated 8.

Table 3. Multivariate logistic regression analysis of factors related to overactive bladder

Categorical variable	Continuous variable	p value	OR	95% CI
	Age (years)	0.053	1.79	0.98-3.27
Smoker		0.846	1.05	0.63-1.74
	BMI (kg/m^2)	0.743	0.99	0.92-1.05
	Heart rate (bpm)	0.082	0.69	0.45-1.06
Diabetes mellitus		0.837	1.04	0.64-1.71
	SYNTAX score	< 0.001	1.47	1.35-9.19

BMI, body mass index; CI, confidence interval; OR, odds ratio.

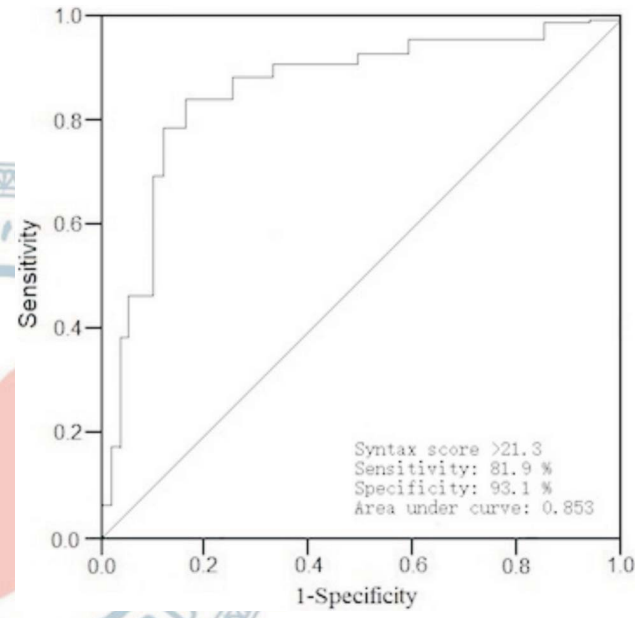

Figure 3. *Diagnostic accuracy of SYNTAX score I in the prediction of overactive bladder.*

age, and OAB is accepted to be one of the most important factors that impairs the quality of life in both genders among the elderly population.[5] Pinggera et al. reported that in the transrectal color Doppler ultrasonography of elderly patients with lower urinary tract symptoms (LUTS), there was a significant decrease in the bladder blood flow compared to asymptomatic young controls, supporting the development of chronic bladder ischemia with aging.[17] The increased incidence of OAB with age is based on this hypothesis.[18] In our study, the age of the group with OAB was statistically higher than that of the group without OAB (66.2 and 58.5 years, respectively; $p < 0.01$), and this confirms the increased incidence of this condition with advanced age.

Atherosclerosis is a multifactorial chronic inflammatory disease that occurs in response to endothelial damage, and mostly affects the intimal layer of arteries with a greater diameter. In at least half of patients with atherosclerosis, the first presentation is often an acute coronary event, which has also been implicated in 68% of sudden deaths.[3] Therefore, the diagnosis and treatment of ischemic heart disease before symptoms appear are vital.[19] Due to its high morbidity and mortality rates, as well as socioeconomic consequences, great efforts have been made for the early detection of coronary artery disease worldwide. Many studies have emphasized that there is a close relationship between erectile dysfunction (ED) and CAD, and some studies have reported that ED occurs at least two to five years before the development of a cardiovascular event, and therefore can be

considered as a precursor of a concealed cardiovascular disease.[20,21] A close relationship has been found between LUTS and chronic diseases, such as hypertension, diabetes, and hyperlipidemia, which are the most important risk factors for CAD.[22] In brief, atherosclerosis is a systemic event, and all arteries in the body are affected by this condition simultaneously. While relatively larger arteries have better tolerance to atherosclerosis-reduced blood flow, narrower arteries, such as coronary, penile and vesicular arteries have lower tolerance and develop clinical symptoms.[23]

The SYNTAX scoring system was developed as a comprehensive angiographic scoring system aimed at assisting patient selection and risk classification in patients scheduled for PCI or coronary artery bypass grafting due to diffuse coronary disease.[24] According to the characteristics of the lesions, the SYNTAX score can identify patients who are good candidates for PCI, classifying them as low-risk (0-22 points), moderate-risk (23-32 points), and high-risk (≥ 33 points). Therefore, it is considered to be a useful scoring system for risk classification.[25] Similarly, we compared the OAB-V8 score between SYNTAX score subgroups in our study, and found that there was a statistically significant difference in the OAB-V8 score between the subgroups.

Although a relationship between atherosclerosis and associated pelvic ischemia and OAB has been reported in various publications in the literature, the cardiac aspect of the current relationship has not been sufficiently explored. We conducted this study to establish a relationship between OAB and CAD based on their common etiological factor of atherosclerosis, and our data supports an association between the two. This study further confirms the importance of OAB and the OAB-V8 questionnaire for the early identification of patients at increased risk of CAD, which could elicit measures to prevent major cardiovascular events in this population.

Our study has some limitations. First, we determined our patient group by questioning subjective complaints such as urgency and nocturia using OAB-V8 score. Second, there were no long-term follow-up data of these patients. In addition, this study did not enroll a healthy control group to demonstrate the differences in OAB by OAB-V8 score between healthy controls and patients with CAD.

CONCLUSION

In this study, the presence of severe OAB symptoms in patients with significantly high coronary artery stenosis emphasizes that urologists and cardiologists should work in collaboration in monitoring the geriatric population and patients with chronic diseases, who we think are predisposed to atherosclerosis. We consider that in this patient population presenting with OAB symptoms, an early cardiology evaluation may help to make an early diagnosis and plan treatment of underlying coronary heart disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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