# Association of Severity of Lower Extremity Arterial Disease and Overactive Bladder Syndrome: A Cross Sectional Study

Bahar Yuksel[1]*, Faruk Ozgor[2], Mazlum Sahin[3], Metin Savun[2],Murat Sahan[2] ,Ufuk Caglar[2],Omer Sarilar[2]

**Purpose:** The aim of this study aim is to clarify the relationship between Overactive bladder syndrome (OAB) and severity of lower extremity ischemia by using Fontaine classification system.

**Materials and Methods:** Patients who were diagnosed with lower extremity arterial disease were enrolled into the study. The Fontaine score of each patient was taken and all patients completed the validated Turkish version of OAB-V8 questionnaire. Body mass index, serum creatinine, blood urea nitrogen, cholesterol and fasting plasma glucose levels were measured. The patients were divided into two groups. Patients with OAB-V8 score above 8 were enrolled into group 1 and patients with OAB-V8 score under 8 were enrolled into group 2.

**Results:** At the end of study period, 181 patients who met the inclusion criteria were enrolled into the study. Patients with OAB □ 8 score (n= 79) were compared with patients with OAB < 8 score (n= 102). The mean age and the mean BMI were significantly higher in patients with OAB ≥ 8 (*P* = .001 and *P* = .001, respectively). Also, HDL- cholesterol level was found significantly lower in group 1 patients (P= .001). Multivariate regression analysis showed that presence of Fontaine score ≥ class 2b, age ≥ 60 years, BMI ≥ 30 kg/m$^2$ , and HDL-cholesterol levels < 60 mg/dL were predictive factors for OAB.

**Conclusion:** The present study demonstrated that incidence of OAB is higher in patients with severe lower extremity ischemic symptoms, older age, high BMI, and lower HDL-cholesterol level.

**Keywords:** atherosclerosis, Fontaine classification, OAB-V8 form, overactive bladder, urgency

## INTRODUCTION

According to the International Continence Society, overactive bladder syndrome (OAB) is a clinical entity including urgency with or without urgency incontinence, frequency and nocturia in the absence of pathological and/or metabolic disorder that may clarify these signs [(1)]. According to literature, the prevalence of OAB has been reported in a wide range up to 53% causing significant deterioration in patients sexual function, mental health, and overall life quality. Although, previous reports have reported several factors including aging, central and peripheral sensory, somatic and peripheral neuropathy, and atherosclerosis , the underlying mechanism has not been understood clearly yet [(2)] . Atherosclerosis (AT) is a course that progressive hardening and thickening of arteries wall forms as a result of fat deposit plaques on their inner lining. Also, AT is a systemic disorder and small-medium size arteries such as iliac artery branches are more vulnerable to atherosclerotic lesions[(3)]. Capple et al. stated that pelvic ischemia due to AT is trigger point for development of lower urinary system symptoms such as urgency, frequency and nocturia[(4)]. On the other hand, AT in the iliac artery and distal branches of iliac artery is associated with lower limb ischemia and lead symptoms including sense of fatigue, numbness, muscle pain, and muscle cramp. To determine severity of peripheral artery ischemia, Fontaine at al. described a classification system including four stages: asymptomatic patients, patients with intermittent claudication, patients with rest pain and patients with ischemic ulcers or gangrene[(5)].
Previous reports have demonstrated the relationship between pelvic ischemia and OAB, however none of these studies has evaluated the presence of OAB in patients with peripheral lower extremity artery ischemia. The aim of this study was to clarify the relationship between OAB and severity of lower extremity ischemia using Fontaine classification system.

## MATERIALS AND METHODS

After obtaining local ethics committee approval, patients diagnosed with lower extremity AT between January 2017 to January 2018 in the cardiovascular unit of a tertiary academic center were enrolled into the study. The research was managed in accordance with Helsinki Declaration and informed consent was obtained from all patients. To achieve indiscrete study population, patients younger than 18 years old, patients with benign prostate hyperplasia, uncontrolled diabetes melli-

[1]Department of Obstetrics and Gynecology, Esenler Maternity and Children's Hospital, Istanbul, Turkey
[2]Department of Urology, Haseki Teaching and Research Hospital, Istanbul, Turkey
[3]Department of Cardiovascular Surgery, Haseki Teaching and Research Hospital, Istanbul, Turkey
*Correspondence: Department of Obstetrics and Gynecology, Esenler Maternity and Children's Hospital, Istanbul, Turkey
Tel: +90 [0212] 440 39 00. Fax: +90 [0212] 440 39 00. E-mail: baharyl86 @gmail.com.
Received October 2018 & Accepted December 2019

**Table 1.** Comparison of patients' characteristics

| | Groups<br>**OAB [Group 1]** | **Non-OAB [Group 2]** | ***p* value** |
|---|---|---|---|
| Number | 79 | 102 | |
| Gender [Male/Female] | 66/13 | 81/21 | .483 |
| Age [years]* | 64.2 ± 8.1 | 56.0 ± 7.9 | .001 |
| BMI [kg/m2]* | 32.3 ± 3.9 | 27.5 ± 3.9 | .001 |
| OAB-V8* | 18.7 ± 5.8 | 3.8 ± 2.1 | .001 |
| OAB WET/OAB DRY | 28/ 51 | NA | NA |
| Total water intake (mL) | 1750 ± 680 | 1320 ± 430 | .001 |
| Total caffeine intake (mL) | 440 ± 280 | 280 ± 120 | .001 |
| Total alcohol intake (mL) | 50 ± 15 | 35 ± 10 | .127 |
| Fontaine Score | .001 | | |
| Class 1 | 1 [1.3%] | 47 [46.1%] | |
| Class 2a | 32 [40.5%] | 55 [53.9%] | |
| Class 2b | 29 [36.7%] | 0 | |
| Class 3 | 15 [19.0%] | 0 | |
| Class 4 | 2 [2.5%] | 0 | |
| HT | 26 [32.9%] | 32 [31.4%] | .827 |
| Smoking | 29 [36.7%] | 32 [31.4%] | .454 |
| LDL, mg/ml* | 130.4 ± 35.8 | 127.1 ± 36.2 | .546 |
| HDL, mg/dl* | 45.1 ± 5.8 | 76.6 ± 32.2 | .001 |
| Cholesterol, mg/dl* | 265.7 ± 89.1 | 243.2 ± 87.8 | .091 |
| Trigliseride, mg/dl* | 163.6 ± 44.2 | 172.0 ± 49.2 | .238 |
| Glucose, mg/dl* | 136.8 ± 28.7 | 137.8 ± 30.0 | .819 |
| Creatinine, mg/dl* | 1.2 ± 0.7 | 1.4 ± 0.9 | .195 |

* Mean ± standard deviation

Abbreviations: NA : not available; $P < 0.05$ : statistically significant difference; OAB: over active bladder; OAB V8: 8- item validated over active bladder syndrome questionnaire score; BMI: Body mass index; mg/dL: milligram per deciliter; HT: hypertension; LDL: low density lipoprotein; HDL: high density lipoprotein

tus, uncontrolled hypertension, neurological disorders, urinary system cancers, and history of pelvic radiation were excluded from the study. Moreover, patients with residual volume > 100 ml and maximum flow rate < 15 ml/s were also excluded. History of incontinence surgery and pelvic organ prolapse surgery, and presence of pelvic organ prolapse at the time of enrollment were other exclusion criteria.

Asymptomatic patients with lower extremity AT and patients with ischemic symptoms (fatigue, numbness, muscle pain, muscle cramp, skin ulcers and tissue loss) due to lower extremity AT were evaluated by a single cardiovascular surgeon in an outpatient setting. Detailed medical history was obtained and physical examination was performed in all patients. The Fontaine score of each patient was evaluated and all patients completed the validated Turkish version of 8- item validated overactive bladder (OAB) questionnaire
(OAB-V8) . Smoking history and body mass index (BMI) were noted. Also, serum creatinine, blood urea nitrogen, cholesterol, HDL- cholesterol, LDL- cholesterol, triglyceride and fasting plasma glucose levels were measured. Moreover, urine culture, urinalysis, sonography of the urinary tract, uroflowmetry, and bladder diary were performed routinely.

The patients were divided into two groups based on severity of OAB symptoms evaluated by OAB-V8 questionnaire. Patients with OAB-V8 score above 8 were enrolled into group 1 and patients with OAB-V8 score under 8 were enrolled into group 2, respectively. The groups were compared according to patients' medical history, severity of lower extremity ischemic symptoms, OAB-V8 scores, serum blood test results, sonography of the urinary tract and uroflowmetry findings.

8- Item Validated Overactive Bladder (OAB) Questionnaire

The form OAB-V8 is a self-reported questionnaire, including 8 queries that evaluate severity of irritative symptoms including urgency, frequency, nocturia and urgency urinary incontinence. A score of 8 and above of the OAB shows significant association with OAB and a score under 8 indicates that diagnosis of OAB is questionable or absent. In this questionnaire, urgency and frequency are accepted as a sudden urge to pass urine and eight or more micturition per day. The nocturia is defined as waking at night to void ≥ 2 times and involuntary leakage with urgency is described urgency urinary incontinence[6].

Fontaine Classification

The Fontaine classification is a clinical classification method to evaluate the severity of peripheral artery disease which includes four stages. Patients with subclinical peripheral artery disease without any symptoms are enrolled in class 1. Patients with intermittent claudication after walking are considered class 2 (2a: Intermittent claudication after more than 200 meters of pain free walking and 2b: intermittent claudication after less than 200 meters of walking). Patients with rest pain and patients with ischemic ulcers or gangrene are grouped in stage III and stage IV, respectively.

### *Statistical Analysis*

The Statistical Package of Social Sciences for Windows (SPSS) version 20 was used for statistical analysis. We divided patients into 2 groups based on their OAB-V8 score. Categorical variables were presented as numbers and percentages and compared with Chi Square test. Continuous variables were presented as means and standard deviations and compared with independent sample t-test. Logistic regression analysis was used to examine the possible association between age, BMI, HDL and Fontaine Score. Statistical significance was considered as a two-tailed $p$ value < 0.05.

**Table 2.** Comparison of patients according to OAB symptoms and uroflow parameters between groups

| | Groups OAB [Group 1] | Non-OAB [Group 2] | *p* value |
|---|---|---|---|
| Number | 79 | 102 | |
| Urgency | 70 [88.6%] | 22 [21.6%] | .001 |
| Frequency | 41 [51.9%] | 20 [19.6%] | .001 |
| Nocturia | 43 [54.4%] | 29 [28.4%] | .001 |
| Urgency urinary incontinence | 42 [53.2%] | 7 [6.9%] | .001 |
| Postvoiding urinary residue, ml* | 42.5 ± 18.4 | 41.9±18.7 | .887 |
| Max flow rate, mL/s* | 20.4 ± 3.4 | 20.7±3.9 | .660 |
| Average flow rate, mL/s* | 13.6 ± 2.4 | 13.5±2.4 | .784 |
| Voided volume, mL* | 200.1 ± 43.8 | 213.1±67.1 | .135 |

* Mean ± standart deviation
$P < 0.05$ : statistically significant difference
**Abbreviation:** OAB: over active bladder

## RESULTS

At the end of one-year study period, 322 patients were enrolled into the study out of which 181 patients met the study inclusion criteria and where included in the final analysis. Due to benign prostate hyperplasia, uncontrolled diabetes mellitus, neurological disease, history of pelvic radiation, history of pelvic organ surgery and usage of medication for OAB, 71, 12, 15, 9, 6 and 19 patients were excluded from the study, respectively. Also, 9 patients were excluded due to other reasons in accordance with study exclusion criteria.

The patients with OAB ≥ 8 score (n = 79) and the patients with OAB < 8 score (n = 102) were compared. The mean age and the mean BMI were significantly higher in patients with OAB≥ 8 ($p = 0.001$ and $p = .001$, respectively). The mean age of patients with wet OAB was higher although the difference was not statistically significant (66.2 vs 62.7, $p = .114$). On the other hand, gender, presence of hypertension and smoking history were comparable between two groups ($p = .483$, $p = .827$ and $p = .454$, respectively). Moreover, levels of serum creatinine, fasting plasma glucose, LDL- cholesterol and triglyceride did not show statistical difference between patients with OAB ≥ 8 and patients with OAB < 8 score. However, HDL- cholesterol levels were found significantly lower in patients in group 1 (45.1 mg/dL vs 76.6 mg/dL, $p = .001$). When groups were compared according to Fontaine classification system, the patients with OAB ≥ 8 score had higher scores ($p = .001$). The mean post voiding volume was 42.5 ml in group 1 and 41.9 ml in group 2 ($p = .887$). Also, the mean maximum flow rate and the mean average flow rate were similar between two groups ($p = .660$ and $p = .784$, respectively). The patient number according to Fontaine classification is listed in **Table 1**.

Multivariate regression analysis showed that presence of Fontaine score ≥ class 2b is an independent risk factor for OAB and increases the risk of OAB upto 4 fold . Additionally, age ≥60 years, BMI ≥ 30 kg/m$^2$ and lower HDL-cholestrol level (60 mg/dL) were predictive factors for OAB (**Table 3**).

## DISCUSSION

Atherosclerosis is a multifocal, smoldering and immune inflammatory disorder that leads to endothelial dysfunction affecting all arteries of the body. It's well known that small and medium sized arteries like penile and vesical arteries are more vulnerable to AT due to their relatively small lumen diameter compared to wider sized arteries. In accordance with this hypothesis, authors showed that the significant relationship between coronary artery disease and erectile dysfunction indicates the possible role of OAB[7,8].

The severity of lower extremity ischemia has been reported in a wide range according the literature due to the subjective examination finding and different interpretation of imaging modalities. Thus, classification systems have been created for more objective evaluation of ischemia, better surgical planning and comprehensive patient counseling. Additionally, using classification system has led to further scientific reporting[9]. The Fontaine classification system is the first determined tool to clarify severity of lower extremity ischemia by European Society of Cardiovascular Surgery. The system is solely based on physical examination and severity of ischemic symptoms classified into stage 1 to 4 [5]. According to artery size hypothesis, patients categorized within a higher Fontaine class, are expected to face bladder ischemia, including OAB syndrome more often. In accordance with that hypothesis, we found significantly higher OAB-V8 score in patients categorized within higher Fontaine class and multivariate analysis

**Table 3.** Univariate and Multivariant Analysis

| | Odds Ratio* | p* | Odds Ratio** | *p*** |
|---|---|---|---|---|
| Agea | 1.9 (1.4-2.6) | 0.001 | 2.5 (1.1-5.6) | .027 |
| BMIb | 2.6 (1.9-3.7) | 0.001 | 4.2 (1.8-9.5) | .001 |
| HDLc | 17.5 (4.5-68.3) | 0.001 | 30.9 (6.7-142.3) | .001 |
| Fontain Scored | 1.3 (0.9-1.9) | 0.002 | 4.0 (1.2-13.5) | .023 |

* univariate analysis
**multivariate analysis
a: < 60 years vs ≥ 60 years
b: < 30 kg/m2 vs ≥ 30 kg/m$^2$
c: < 60 mg/dl vs ≥ 60 m/dL
d: < Grade 2b vs ≥ Grade 2b

revealed classification as Fontaine 2b or higher is an independent risk factor for OAB development.

The incidence of atherosclerosis increases with age, it reduces blood flow and corrupts oxygenation of tissues. Pinggera et al. compared bladder perfusion of 32 elderly patients which have lower urinary tract symptoms and 20 young healthy volunteers with transrectal colour Doppler ultrasonography. They found significantly lower bladder perfusion rate in symptomatic elderly patients than in the younger healthy volunteers[10]. In a more recent study by Kilinc et al. age was identified as independent risk factor for OAB development in multivariate regression analysis[11]. In accordance with studies mentioned above, we also determined a statistically significant relation with age and OAB in the present study.

Several authors had stated that prevalence of OAB syndrome has a positive correlation with obesity due to increased intraabdominal and intravesical pressure that leads overactivity of detrusor muscle. Richter et al. claimed high abdominal pressure may deteriorate innervations of pelvic floor[12]. In another possible hypothesis, ghrelin-A peptide hormone that regulates metabolic activity and reach higher levels in obese patients may be the other trigger causing an increase on contractile activity of the bladder through its receptors on preganglionic neurons[13]. Moreover, relationship between obesity and AT risk factors such as dyslipidemia, hypertension, insulin resistance is well known. In this present study, we found significantly higher BMI in patients who were diagnosed OAB syndrome and BMI ≥ 30 kg/m2 increased OAB syndrome risk 4.2 fold times. However, we did not find any association between other AT risk factors and OAB syndrome. Our study sample may justify these results since only patients whose diabetes mellitus and hypertension were under control were included into study. We found higher LDL- cholesterol levels in patients with OAB. However, univariate analysis did not predict LDL-cholesterol as risk factor for OAB development. However, we did not evaluate the possible effect of dyslipidemia duration and central obesity in the OAB development. These may be a subject of another study.

Plasma lipids have crucial role in AT development. The one of cholesterol subtype called as HDL cholesterol facilitates promotion of reverse cholesterol transport, accelerates plaque regression, and leads to endothelial function improvement. Moreover, HDL has anti-inflammatory and anti-thrombotic characteristics. Thus, some authors hypothesize that increase in HDL levels may be associated with reduction of AT events[14]. In accordance with that knowledge, we found significant higher HDL- cholesterol levels in patients without OAB (76.6 mg/dL vs 45.1 mg/dL, $P$ = 0001, respectively). Moreover, multivariate regression analysis revealed higher HDL- cholesterol level as a predictive factor to prevent OAB. However, some studies emphasized the HDL- cholesterol functionality is more important to prevent AT event beyond plasma HDL-cholesterol concentration. Correlation between OAB and HDL- cholesterol functionality may be a subject of another study.

The present study has some limitations. First, our study was a cross sectional study with a relatively small patient number. Additionally, this study included patients from only a single center and represented only single center experience. However, all patients were evaluated by a single cardiovascular surgeon and urologist that improve internal validity of the study. Also, we could not evaluate the interval time between the beginning of ischemic symptoms and OAB symptoms. Lastly, we did not analyze the treatment response and treatment cost of patients who referred to outpatient urology clinic from the cardiovascular unit.

The present study demonstrated that incidence of OAB was higher in patients with severe lower extremity ischemic symptoms. Additionally, patients with older age, high BMI and lower HDL-cholesterol level face OAB symptoms more frequently. Our study supported that investigating bladder function is advisable in patients with severe leg ischemia. Our findings must be supported by further prospective studies with a larger patient volume.

## CONFLICT OF INTEREST

None declared by the authors.

## REFERENCES


1. Azurı J, Kafri R, Ziv-Baran T, Stav K. Outcomes of different protocols of pelvic floor physical therapy and anti-cholinergics in women with wet over-active bladder: A 4-year follow-up. Neurourol Urodyn , 2017; 36.3: 755-8.
2. Bykoviene L, Kubilius R, Aniuliene R,Bartuseviciene E, Bartusevicius A. Effects on The Overactive Bladder. A Randomized Clinical Trial. Urol J. 2018;15: 186-192.
3. Herrington W, Lacey B, Sherliker P. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. Circ Res 2016; 118:535–46
4. Chapple C (2014) Chapter 2: Pathophysiology of neurogenic detrusor overactivity and the symptom complex of “overactive bladder”. Neurourol Urodyn 33(Suppl 3): S6–S13.
5. Novo S., Coppola G. Milio G. Critical limb ischemia: definition and natural history. Current Drug Targets-Cardiovascular & Hematological Disorders, 2004; 4.3: 219-25.
6. Tarcan T, Mangir N, Ozgur MO et al. OAB-V8 overactive bladder questionnaire validation study. Üroloji Bülteni 2012; 21:113–6
7. Montorsi P, Ravagnani PM, Galli S. Association between erectile dysfunction and coronary artery disease: matching the right target with the right test in the right patient. Eur Urol, 2006; 50:721–31
8. Acquadro C, Kopp Z, Coyne KS, Corcos J, Tubaro A, Choo MS. Translating overactive bladder questionnaires in 14 languages. Urology, 2006; 67: 536-40.
9. Ozgor F, Yanaral F, Savun M, Ozdemir H, Sarilar O, Binbay M. Comparison of STONE, CROES and Guy’s nephrolithometry scoring systems for predicting stone-free status and complication rates after percutaneous nephrolithotomy in obese patients.

Urolithiasis, 2017; 1-7.

10. Pinggera G, Mitterberger M, Steiner E et al Association of lower urinary tract symptoms and chronic ischaemia of the lower urinary tract in elderly women and men: assessment using colour Doppler ultrasonography. BJU Int 2008; 102:470–4
11. Kilinc MF, Yasar E, Aydin HI, Yildiz Y, Doluoglu OG. Association between coronary artery disease severity and overactive bladder in geriatric patients. World J Urol, 2018; 36:35-40.
12. Richter HE, Creasman JM, Myers DL, Wheeler TL, Burgio KL, Subak LL. Urodynamic characterization of obese women with urinary incontinence undergoing a weight loss program: the Program to Reduce Incontinence by Diet and Exercise (PRIDE) trial. International Urogynecology Journal, 2008; 19:1653-8.
13. Ferens, D. M., Yin, L., Ohashi-Doi, K., Habgood, M., Bron, R., Brock, J. A.,Furness, J. B. . Evidence for functional ghrelin receptors on parasympathetic preganglionic neurons of micturition control pathways in the rat. Clinical and Experimental Pharmacology and Physiology, 2010;37 :926-932.
14. Zhou P, Li B, Liu B, Chen T, Xiao J. Prognostic role of serum total cholesterol and high-density lipoprotein cholesterol in cancer survivors: A systematic review and meta-analysis. 2018; 477:94-104.