An examination of relationship between overactive bladder and C-reactive protein and erythrocyte sedimentation rate

Aşırı aktif mesane ile C-reaktif protein ve eritrosit sedimantasyon hızının ilişkisi

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Özet

Amaç: Hastaların yaşam kalitesini olumsuz olarak etkileyen aşırı aktif mesanenin (OAB) kesin nedeni bilinmemektedir. Bu çalışma bugüne kadar etyolojisi tam olarak aydınlatılamayan OAB'li hastalarda inflamatuar sürece ilişkin kanıtlar sağlamak amacıyla planlandı.

Gereç ve Yöntemler: Çalışmaya OAB tanısı alan 154 kişi ile kontrol için kullanılan 131 kişi kaydedildi. Çalışma Nisan 2015 ile Nisan 2020 yılları arasında retrospektif, kesitsel olarak yapıldı. Veriler bu konuda uzman bir kişi tarafından, ilk görüşmede kaydedildi. Gruplar serumda ölçülen CRP ve ESR açısından karşılaştırıldı. İstatistiksel analizde Ki-kare testi, Bağımsız örneklemler t-testi, Mann-Whitney U testi, Pearson ve Spearman korelasyon analizleri kullanıldı. P<0.05 düzeyi istatistiksel olarak anlamlı kabul edildi.

Bulgular: Gruplar arasında ek hastalıklar açısından farklılık saptanmadı. Yaş ve BMI açısından gruplar arasında anlamlı farklılık saptandı (p<0.005). Gruplara göre CRP düzeyleri karşılaştırıldığında, OAB grubu için 0.28 [0.54] ve kontrol grubu için 0.17 [0.22] mg/dl olarak saptandı (p=0.047). ESH'nın gruplara göre dağılımı sırasıyla için 19 [30.5] ve 12.5 [13] mm/h olarak izlendi (p=0.004).

Sonuç: Bu çalışma OAB ile inflamatuar bir süreç arasındaki ilişkiyi gösteren bilgilerimize yeni kanıtlar sunmaktadır. OAB'li hastalarda CRP ve ESH düzeylerinin kontrol grubuna göre arttığı saptandı. Bu sonuçlar bize bu hastalığın temelinde inflamatuar bir sürecin olduğunu göstermektedir.

Anahtar Kelimeler: inflamasyon, aşırı aktif mesane, C-reaktif protein, eritrosit sedimantasyon hızı

Abstract

Objective: The definite cause of overactive bladder (OAB), which negatively affects the quality of life of patients, is unknown. This study aims to provide evidence for the inflammatory process in patients with OAB whose etiology has not been fully elucidated.

Material and Methods: The study included 154 people with OAB diagnosis and 131 people as controls. This study was conducted retrospectively, cross-sectionally between April 2015 and April 2020. The data were recorded at the first meeting by an expert on this subject. Groups were compared in terms of CRP and ESR measured in serum. Statistical analysis used the chi-square test, independent samples t-test, Mann-Whitney U test, and Pearson and Spearman correlation analyses. P<0.05 was accepted as statistical significance.

Results: There were no differences between the groups in terms of comorbid diseases. There were significant differences identified in terms of age and BMI between the groups (p<0.005). When groups are compared according to CRP levels, values were 0.28 [0.54] for the OAB group and 0.17 [0.22] mg/dl for the control group (p=0.047). The distribution according to ESR in the groups was 19 [30.5] and 12.5 [13] mm/h, respectively (p=0.004).

Conclusion: This study provides new evidence to the literature showing the relationship between OAB and an inflammatory process. It was determined that CRP and ESR levels were increased in patients with OAB compared to the control group. These results show us that there is an inflammatory process at the onset of this disease.

Keywords: inflammation, overactive bladder, C-reactive protein, erythrocyte sedimentation rate

The study was approved by Ordu University Ethics Committee of Clinical Researches (Approval No: 2021-54, Date: 2021/03/04). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Overactive bladder (OAB) is a pathology characterized by urgency accompanied, or not, by urine leakage, without any pathology like urinary tract infection (UTI) or diabetes. It is frequently accompanied by increased urination frequency during the day or at night (1). Despite the difficulty in identifying the definite incidence of this disease in society, it is thought that the rate is 5-10% in the general population and about 16% in young women (2). It negatively affects daily life.

Though it is frequently considered that detrusor hyperactivity causes OAB in patients, no underlying cause can be identified in many cases (3). The most important problem related to this disease is the lack of a specific diagnostic tool or marker for this disease at present. Commonly diagnosis is made by excluding other pathologies causing irritative bladder symptoms. The only objective evidence at hand is urination diaries and survey forms. Disease diagnosis may be placed fully with subjective complaints. To date, the underlying cause has not been fully understood. However, in recent times, the number of studies attracting attention to the association of OAB with inflammation has increased (4). The reason for the lack of full explanation about this disease to date may be due to the deficiency of diagnostic tests that can be used (5). A study supporting this viewpoint reported that symptoms improve when antibiotic treatment is administered even without visible infection factors in urine (6). In conclusion, inflammation may be a cause underlying this disease. These findings increased hopes of finding a specific marker for this disease.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are markers frequently used for inflammatory events. CRP is an acute phase protein induced by proinflammatory cytokines, like interleukins. It is synthesized by liver cells in the presence of inflammatory disease (7). It is considered to be a defense against inflammatory agents in the body. Limited studies are using CRP for OAB patients and CRP levels in OAB patients are reported to be high compared to controls (8). However, data is not adequate to recommend routine use. To the best of our knowledge, there is no study in the literature about the other inflammatory marker of ESR.

This study was planned to compare the systemic inflammatory markers of CRP and ESR, accepted as prognostic markers in many diseases, in OAB patients with a control group. Our essential aim in this study is to provide evidence related to the inflammatory process for this disease with etiology not fully explained to date.

MATERIAL AND METHODS

Research Design

The study included a total of 285 sequential patients attending the urology clinic from April 2015 to April 2020 abiding by the study criteria including 148 women and 137 men.

The study was made cross-sectional with a retrospective review of data from prospectively enrolled patients. The study registered 154 people with OAB diagnosis and 131 people as controls. OAB diagnosis used urgency and increased urination frequency accompanied or not by urine leakage as criteria (1). The laboratory tests of the patients were collected at the first meeting. This diagnosis was used after excluding other underlying pathologies like UTI. If there were an underlying cause like UTI, the patient would be assessed after the treatment. Patients were assessed by an expert on this topic and prospectively registered. The control group was formed from the relatives of the patients who have any known complaint. The study was conducted in adherence to the Declaration of Helsinki. The study protocol was approved by a local ethics committee (Ordu University Clinical Research Ethics Committee, Approval Number: 2021/54, Date: 2021/03/04).

Diabetes mellitus, presence of systemic infection, chronic urinary tract infection, bladder stones, bladder cancer, neurologic diseases, and other situations that may cause OAB symptoms were used as exclusion criteria. Additionally, patients with surgical histories due to urinary incontinence or any other pelvic pathology were not included in the study. Patients with renal failure, lymphoma-myeloproliferative and hemolytic dis-

eases that may affect blood values were excluded from the study. Patient age, body mass index (BMI), waist circumference, OAB survey form, quality of life score (QoL), urinary complaints, and comorbid diseases were recorded. The forms used in the study were filled by the patient. OAB form consists of 8 questions. For each question, the patient gives points between 0-5. The total score is obtained by adding the points given to the questions (2 points added for men). Above 8 points is considered significant. For QoL, the 8th question of the IPSS inquiry form was used. Likewise, it was scored between 0 and 5. Serum c-reactive proteins and erythrocyte sedimentation rate results were recorded.

Statistical Analysis

Parameters with normal distribution are given as mean ± SD, and parameters without normal distribution are given as median ± interquartile range (IQR). The Kolmogorov-Smirnov test was used to examine the normal distribution of data. To compare the group differences, a student t-test for parametric data analysis and a Mann-Whitney-U test for nonparametric data. Correlation analysis used the Pearson test for parametric data and the Spearman chi-square test for nonparametric data. All statistical analyses were performed with the "SPSS for Windows version 20.0" program. P values <.05 were accepted as significant.

RESULTS

The study registered a total of 285 people, with 148 (51.9%) females and 137 (48.1%) males. The control group included 131 patients (46%) and the OAB group included 154 patients (54%). The control group comprised 58 women (44.3%) and 73 men (55.7%), while the OAB group comprised 90 women (58.4%) and 64 men (41.6%) (p=0.017). The mean ages in the groups were 60.97±12.29 years in the OAB group and 56.09±8.71 years in the control group (p=0.001). When groups are compared in terms of body weight, values were 82.49±14.76 and 81.02±14.63 kg in group 1 and group 2, respectively (p=0.408). In terms of BMI, values were 30.81±5.49 and 29.47±5.21, respectively (p=0.039). There were no significant differences identified between the groups in terms of comorbid diseases such as hypertension, heart disease, and diabetes (Table 1).

Comparing the groups by CRP levels, the observed values were 0.28 [0.54] in the OAB group and 0.17 [0.22] mg/dL in the control group (p= 0.047). The distribution of ESR in the groups was 19 [30.5] and 12.5 [13] mm/h, respectively (p= 0.004) (Table 2).

Table 1. Distribution of demographic characteristics

Characteristics	Groups		P-value
	OAB (Group 1)	Control (Group 2)	
Age (year)	60.9±12.2[a]	56.09±8.7[a]	0.001*
Body weight (kg)	82.4±14.7[a]	81.03±14.6[a]	0.408
BMI (kg/height[2])	30.8± 5.4[a]	29.4± 5.2[a]	*0.039**
Hypertension n (%)[b]	86 (56.6)	62 (47.7)	0.136
Dyslipidemia n (%)[b]	90 (60.4)	83 (64.8)	0.447
Heart disease n (%)[b]	33 (22.1)	19 (14.6)	0.107
Diabetes n (%)[b]	53 (34.9)	35 (26.9)	0.151
Neurologic disease n (%)[b]	20 (513.4)	13 (10)	0.377
Pulmonary disease n (%)[b]	22 (14.9)	10 (7.7)	0.062
Psychological problems n (%)[b]	41 (27.3)	35 (26.9)	0.939

*[a] = mean ± SD, [b]: Within grup, * = Statistically significant (Student's t-test)*

Table 2. Comparison of urinary complaints and inflammatory parameters in the groups

Features	LUTS Group		p-value
	OAB (Group 1)	Control (Group 2)	
CRP mg/dl	0.28 [0.54][a]	0.17 [0.22][a]	0.047*
ESR mm/h	19 [30.5][a]	12.5 [13][a]	0.004*
Frequency of daytime urination	8 [5][a]	4 [4][a]	<.001*
Frequency of nighttime urination	4[4][a]	1[1][a]	<.001*
Urine leakage n (%)	106 (99.1)	1 (0.9)	<.001*
OAB total score	14[6][a]	6[7][a]	<.001*
QoL score	1[3][a]	0[1][a]	<.001*

a*= median [IQR], * = Statistically significant (Mann- Whitney U testi)*

DISCUSSION

This study aimed to investigate whether there is a correlation between inflammatory parameters associated with many pathologies and OAB or not. The results of the study identified an association of OAB with CRP and ESR indicating that OAB is associated with the inflammatory process.

Epidemiological studies showed that urinary complaints including OAB increase with age in men and women (9). Consistent with the literature, our study results indicate that the incidence was increased in both genders by age and OAB patients had higher mean age compared to the control group. The daily life of patients is negatively affected and these problems include embarrassment, disrupted social relationships, sexual problems, and psychological problems (10).

The underlying cause has not been discovered exactly. Obesity is among the most frequently blamed causes. Lawrence et al. reported that OAB incidence increased by 2 times in obese women compared to non-obese women (11). Somestudies have found a link between obesity and OAB (12). Our results showed that the BMI in the OAB group was increased compared to the control group, compatible with the literature. The mechanism by which obesity causes urinary complaints has not been definitively revealed. In these patients, the commonly observed metabolic syndrome and related inflammatory process may trigger OAB development (13).

The present study showed that CRP and ESR increase in OAB patients compared to the control group indicating an inflammatory process as the basis of this disease. One probable reason for diagnosing this disease may be that there is no specific indication or diagnostic test for this disease. In other words, the existing inflammatory process may be missed. These patients visit the hospital with similar complaints and suffer from diseases such as UTI and bladder cancer including urgency and frequent urination. Diagnosis is made by excluding underlying pathologies. In our current practice, UTI diagnosis uses mid-flow urine cultures frequently, and >105 CFU/ml proliferation in these cultures which is accepted as significant. This test involves questions about the efficacy to show bacteria existing in the urinary tract. In a similar study by Khasriya et al., it was observed that patients with chronic urinary tract complaints for 3 years. The study found a presence of bacteria with intracellular colonization which could not be observed by classic tests. These bacteria only proliferated in sediment cultures including urothelial cells. They recommended the need for a threshold value of >102 CFU/ml for the identification of infection (5). This result indicates that the urine analysis routinely used for patients with urinary complaints is not adequate. These results were supported by Walsh et al. who reported that low-count bacteriuria frequency increased in OAB patients and that the existing infection in these patients may be overlooked due to the threshold value (14). A study observed more frequent microscopic pyuria and infected urothelial cell numbers that may be related to urinary symptoms in OAB patients compared to a control group (15). There is other evidence showing difficulties experienced in detecting the existing infection in this patient group.

A study administered combined antibiotic therapy including gram-negative and gram-positive bacteria to OAB patients and reported improved perceptions related to symptoms and bladder problems in patients after treatment (6). In OAB patients, the occurrence of low cystometric volumes may be related to increased bladder afferent sensitivity causing bladder fullness and urgency feeling (16). Proinflammatory agents occurring during inflammation may directly sensitize the afferent nerve endings (17). A study by Furuta et al. showed increased proinflammatory mediators in OAB patients (18). Neonatal bladder inflammation induced in rats resulted in OAB-like excessive response to inflammatory stimuli in adults (19). In recent times, the observation of specific microbiome presence in the bladder, as in the intestines, supports the information above. An association was reported between the known pathology of irritable bowel syndrome (IBS) and disrupted intestinal flora (20). This association may be present in the bladder with chronic urologic diseases like OAB. A study on this topic compared OAB and IC patients with known chronic bladder disease with a control group. The results of the study reported that there was variability in the bladder microbiome of patients and that OAB and IC patients had reduced lactobacilli numbers compared to the control group (21). The deficiency of Lactobacillus acidophilus was associated with an increased interstitial cystitis symptom score index and high pain score (22). Another study supporting this reported more frequent observation of the significant urinary pathogen of Proteus in lower urinary tract symptoms and OAB patients compared to a control group (5).

Briefly, the close association between inflammation and OAB is observed. The use of some markers to show this inflammatory process may contribute to diagnosis and treatment stages. When there is acute or chronic inflammation in any area of the body, inflammatory agents like interleukin-6 increase in blood. The liver releases acute phase proteins like CRP into the blood in response to this inflammatory material (7). Measurement of this material in serum provides important information related to inflammation.

CRP and ESR have frequently used laboratory tests for systemic inflammatory diseases (23). They provide important information to monitor the inflammatory process. There are limited studies investigating the association between systemic inflammatory markers like CRP and ESR with OAB. Although some studies have investigated the relationship between mainly CRP with OAB has been investigated, there is no study related to ESR to the best of our knowledge. Therefore, more studies are needed to uncover the uncertainty about this topic. In this sense, this study aims to bridge this research gap by examining the systemic dimension of the relationship between OAB and inflammation.

CRP may be considered response or defense of the body against inflammatory agents. CRP is frequently used as a marker for acute and chronic inflammatory diseases. It begins to increase 4 hours after injury and peaks within 24-72 hours. Studies associated CPR with many pathologies with an inflammation background. In a study we performed, it was identified to be associated with PSA (24). Apart from this, associations with cancer and cardiovascular diseases were shown (25). More interestingly, an association between CRP with urinary symptoms, including storage symptoms especially, was reported. A study on this topic reported a correlation between increased CPR levels with storage symptoms in males over 40 years (8). A study by Kupelian et al. supports this result. In this study, the correlation between storage symptoms with CRP was illustrated for both men and women (26).

ESR is an acute phase reactant used for a long time as a marker. Proteins like increased fibrinogen, clotting proteins, and alpha globulin determine the sedimentation rate during inflammation. Compared with ESR, CRP is a more sensitive and specific marker (27). However, ESR is known to be more effective in some situations, like low-level bone and joint infections (28). Many studies investigated its diagnostic performance. Most studies come from orthopedic surgeons. Hanada et al. compared ESR and CRP levels in osteoarthritic cases considered to involve background inflammation with a control group. Increased ESR and CRP levels were reported in the arthritis group (29). A meta-analysis investigated the specificity and sensitivity of ESR and CRP for orthopedic infections. In this study, values were 78% and 68% for ESR and 79% and 70% for CRP, respectively (23). It was reported they were beneficial for inflammatory processes in

this study. To the best of our knowledge, the correlation between ESR and OAB has not been investigated.

This study has the feature of being the first study investigating OAB with both CRP and ESR. The results of the study identified an association of OAB with CRP and ESR. These results show that the inflammatory process may be effective in the initiation or worsening of OAB disease. Overactive bladder is a pathology encompassing very complicated processes involving bladder urothelium, bladder sensory nerves, and the central nervous system. The pathology causing this disease has not been explained to date. It is important to identify the underlying causes in terms of revealing safer and more effective treatment choices. Infection beginning in the urothelium causes increased urothelial permeability and may cause proinflammatory matter in urine and the environment to pass into the detrusor. Thus, excess stimulation of sensory nerves found in the detrusor may cause OAB symptoms.

Some limitations need to be reported. First, this study is retrospective in nature. Next, CRP and ESR values were only measured once, and results obtained at different times are not known. Finally, variations after treatment are not known. However, the present study is one of the few studies assessing CRP and ESR together in OAB patients to the best knowledge. Further, the results were reflected in clinical practice and registration of adequate numbers by an expert in this topic.

CONCLUSION

This study provides a piece of evidence supporting the association between OAB and the inflammatory process. It was observed that there was a slight increase in CRP and ESR levels in OAB patients compared to the control group. These results show that the basis of this disease is the inflammatory process.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Ordu University Clinical Research Ethics Committee (Approval Number: 2021/54, Date: 2021/03/04) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design, Data acquisition, Data analysis and interpretation, Drafting the manuscript, Critical revision of the manuscript for scientific and factual content, Statistical analysis, Supervision; Benli E.

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