

## Relationship Between Oxidative Stress and Detrusor Overactivity: A Case Control Study

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**Purpose:** We analyzed the role of oxidative stress in detrusor overactivity (DO) by measuring serum total antioxidant capacity (TAC), total oxidant status (TOS), binding capacity of exogenous cobalt to human albumin (IMA), serum advanced oxidation protein products (AOPP), paraoxonase (PON), and arylesterase.

**Materials and Methods:** The study included 38 female patients diagnosed with DO and 29 healthy female subjects forming the control group. Serum total antioxidant capacity (TAC), total oxidant status (TOS), binding capacity of exogenous cobalt to human albumin (IMA), serum advanced oxidation protein products (AOPP), paraoxonase (PON), and arylesterase were analyzed. The results of serum TAC, TOS, IMA, AOPP, PON, and arylesterase of the subjects in both groups were compared.

**Results:** There was no difference between the groups in terms of age. When compared to the control group, serum TAC and IMA levels were statistically lower ( $P < 0.001$ ) and higher ( $P = 0.003$ ), respectively. However, TOS, AOPP, PON, arylesterase levels were similar in both groups ( $P > 0.05$ ).

**Conclusion:** There seems to be an association between DO and oxidative damage according our results, this can be measured by analyzing TAC and IMA in this patient group.

**Keywords:** detrusor overactivity; hypoxia; ischemia; oxidative stress; total antioxidant capacity

## INTRODUCTION

Detrusor overactivity (DO) is a common distressing condition with an unknown etiology that affects both genders.<sup>(1,2)</sup> Many pathophysiological mechanisms that could cause this condition have been investigated, including oxidative damage and free radicals originating from decreased blood flow, ischemia, and hypoxia.<sup>(3-5)</sup> It has been proposed that free oxygen radicals are involved in this pathophysiological process. Oxidative stress damages the muscarinic receptor-linked signaling system and affects detrusor muscle contractions.<sup>(6,7)</sup> The resulting hypoxia and pelvic ischemia increases the frequency of spontaneous bladder contractions.<sup>(8,9)</sup> Since separate measurements of different antioxidant and oxidant molecules are not efficient in terms of cost and time, total antioxidant capacity and total oxidant status (TAC and TOS, respectively)<sup>(10,11)</sup> can be evaluated in order to demonstrate the individual effects of these molecules. The binding capacity of exogenous cobalt to human albumin (IMA), serum advanced oxidation protein products (AOPP), paraoxonase (PON),

and arylesterase are the best known and most frequently studied antioxidant molecules.<sup>(12-18)</sup>

To the best of our knowledge, there are no studies in the literature focusing on the association of these biomarkers with DO. In the current study, the levels of serum TAC, TOS, PON, arylesterase, AOPP, and IMA of DO patients and healthy controls were investigated and compared. Based on these results, this study presents the characteristics of a preliminary report analyzing the role of ischemia-related oxidative stress in DO.

## MATERIALS AND METHODS

This study was approved by the institutional review board, and patients' consent for the use of their information was taken in writing. The study group consisted of 38 female patients admitted to the Ankara Ataturk Training and Research Hospital Urology outpatient clinic between March 2017 and October 2018 and diagnosed for the first time with DO and 29 healthy female subjects forming the control group. In the DO group, the patients had complaints regarding an increase in

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**Table 1.** The comparison of oxidative parameters between patients with detrusor overactivity and healthy controls.

|      | Group                          | N  | Mean ± S.D        | P-value ( Student T test)              |
|------|--------------------------------|----|-------------------|--|
| Age  | C                              | 29 | 42.7 ± 10.6       | 0.531                                  |
|      | DO                             | 38 | 44.6 ± 14.8       |  |
| TAC  | C                              | 29 | 2.1 ± 0.216       | < 0.001                                |
|      | DO                             | 38 | 1.8 ± 0.199       |  |
| TOS  | C                              | 29 | 4.1 ± 1.46        | 0.109                                  |
|      | DO                             | 38 | 4.7 ± 1.77        |  |
| ARES | C                              | 29 | 189.7 ± 55.7      | 0.662                                  |
|      | DO                             | 38 | 184.6 ± 39.2      |  |
| AOPP | C                              | 29 | 138.9 ± 46.0      | 0.641                                  |
|      | DO                             | 38 | 134.4 ± 32.6      |  |
| IMA  | C                              | 29 | 0.530 ± 0.117     | 0.003                                  |
|      | DO                             | 38 | 0.614 ± 0.106     |  |
|      | <b>Median(25%-75% Quartel)</b> |    |                   | <b>P values ( Mann Whitney U Test)</b> |
| PON  | C                              | 29 | 158.6(91.1-280.8) | 0.934                                  |
|      | DO                             | 38 | 144.1(91.6-249.5) |  |

**Abbreviations:** C, Control group; DO, Detrusor Overactivity group; TAC, Total Antioxidant capacity; TOS, Total Oxidant Status; ARES, Arylesterase; AOPP, Serum advanced oxidation protein products; IMA, Binding capacity of exogenous cobalt to human albumin; PON, Paraoxonase;

daytime (>9 times/day) and nighttime urinary frequency, urgency, and urge incontinence. In order to eliminate other diseases presenting with idiopathic overactive bladder in the differential diagnosis of DO, an overall physical examination, urinalysis, routine biochemical analysis, and detailed laboratory tests, including a urine culture, were performed. Additionally, blood samples were obtained after overnight fasting in order to evaluate oxidative stress status and antioxidant parameters. Samples were drawn from the median cubital vein into blood tubes and immediately stored on ice at 4°C. Serum was separated from the cells by centrifugation at 1000 g for 10 min and then analyzed. In patients with an increase in urinary frequency, urgency, or urge incontinence, urodynamic analyses were done, and those that were diagnosed with DO were included in the study. Patients were excluded from the study if they were using alcohol, tobacco, taking any medication(s), or had systemic diseases since these factors can affect oxidative status. For patients in the DO group, oral solifenacin succinate treatment was started at a daily dose of 10 mg.

Measurement methods of PON, arylesterase, TOS, TAC, AOPP, and IMA were performed in the same manner that was described in our previous study.<sup>(19)</sup>

### Statistical analysis

The sample size of this study was determined using a power analysis. G-Power software was used in this analysis. The power of the study was calculated as 86% when groups 1 and 2 consisted of 38 and 29 participants, respectively. The normal distribution of the oxidative stress biomarkers was evaluated by the Kolmogorov-Smirnov test. Mean ± standard deviations and median (25%–75% quartile) were used for descriptive statistics. Student's t- and Mann Whitney U tests were used for statistical analyses. The data were analyzed by using SPSS for windows (version 25.00).

## RESULTS

**Table 1** summarizes the comparison of oxidative parameters between patients with detrusor overactivity and healthy controls. There was no difference between

the DO and control groups in terms of age. No statistically significant differences were observed between the two groups in terms of the PON ( $P = 0.934$ ), TOS ( $P = 0.109$ ), ARES ( $P = 0.662$ ), and AOPP ( $P = 0.641$ ) levels. When compared to the control group, TAC was significantly lower ( $P < 0.001$ ), and IMA was significantly higher ( $P = 0.003$ ) in the DO group.

## DISCUSSION

Reactive oxygen radicals are produced during the final stages of metabolic and physiological processes. During these processes, harmful oxidative reactions, which are counteracted or detoxified by enzymatic and non-enzymatic oxidative mechanisms, can develop. When an increase in oxidant agents and decrease in antioxidants cannot be prevented, an imbalance occurs between the oxidants and antioxidants, resulting in oxidative stress, which has been shown to be responsible for more than a hundred of diseases.<sup>(19)</sup> Current evidence suggests that oxidative stress plays an important role in the pathogenesis of urinary dysfunction.<sup>(20)</sup>

The prevalence of lower urinary tract symptoms (LUTS) in both genders increases with age. It has been suggested that the arterial occlusive disease, which can lead to chronic bladder ischemia and oxidative damage, has a role in the pathogenesis of lower urinary tract dysfunction, including DO.<sup>(21,22)</sup> Using a rabbit model, Azadzo et al. investigated the association between LUTS and atherosclerotic vascular risk factors and showed that pelvic ischemia caused smooth muscle alterations and denervation in the prostate, penis, and urinary bladder.<sup>(23)</sup> These smooth muscle alterations and denervation induces the frequency of spontaneous bladder contractions and results in DO. Similarly, Nomiya et al.<sup>(22)</sup> investigated the effects of chronic bladder ischemia on voiding behavior and bladder function in rats and reported a significant increase in the rats' urination frequency via cystometric evaluations. The authors concluded that atherosclerosis-induced chronic bladder ischemia could facilitate the voiding reflex, which is defined as DO. In our study, we tried to find an association between DO and oxidative stress by analyzing biomarkers rather than doing histological evaluations. Malona et al.<sup>(3)</sup> reported that oxidative stress was high-

er in the bladder strips of the rats in which in vitro ischemia/reperfusion had been applied and that bladder dysfunction occurred due to oxidative damage. In another study, serum IMA levels were found to have increased in ischemia-induced oxidative stress. The authors also suggested that the IMA levels increase as a result of endothelial and extracellular hypoxia, acidosis, free radical damage, and free iron and copper ions.<sup>(17)</sup> Therefore, IMA was proposed as a marker indicating ischemia.<sup>(17)</sup> Similarly, in the current study, serum IMA levels were found to be higher in the DO group compared to healthy subjects, which support the conclusions of previous studies in which serum IMA levels were used as a marker of ischemia. These studies also support the hypothesis that ischemia is an important factor in the etiology of DO.

To date, there are no studies attempting to find an answer to the association between DO and oxidative stress in humans. The studies were performed in animal models, including rabbits and rats. In 2011, Lin et. al. reported that there was a significant decrease in plasma TAC levels in rabbits having partial bladder outlet obstruction. However, our study included patients with DO, such as the aforementioned group, and we found that TAC levels were statistically lower in patients having DO when compared to healthy subjects.<sup>(24)</sup>

The concentrations of many antioxidants can be measured separately using complicated laboratory techniques, which are time-consuming, labor-intensive, and not cost-effective. Since this is not practical in routine practice, and the antioxidant effects of these molecules are additive, a commonly used alternative is the TAC measurement. Using a serum TAC analysis, the imbalance between oxidants and antioxidants in diseases and the overall oxidative status of the subjects can be clearly demonstrated. In the current study, TAC levels were found to be reduced in the DO group compared to the healthy subject group. This supports the association between oxidative stress and DO.

Despite the considerable amount of research in this area, the etiology of DO has not yet been clearly identified. However, in this study, the mechanism of hypoxia-induced oxidative damage seems to be prominent. Currently, the most effective therapy for DO consists of anticholinergic drugs.<sup>(25)</sup> Identifying the role of ischemia-induced oxidative stress in the etiopathogenesis of DO can contribute to development of alternative treatment options for the disease, such as eliminating the need for lifetime use of medication.

There are several limitations to this study. First of all, our study was a case control study and based on a small sample size. We think that the level of evidence in the study increased since it was designed in a randomized prospective manner, and the finding of oxidative stress was supported by histopathological evaluation. Another limitation could be the lack of biomarker evaluation in the urine samples.

## CONCLUSIONS

The results showed that there was an association between oxidative stress and DO. Thus, oxidative stress biomarkers can be easily evaluated in patients with DO. We found that serum TAC and IMA levels were statistically lower and higher, respectively, when compared with healthy subjects.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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