Research Article

Zeynep Şahiner*, Funda Eren, Salim Neşelioğlu, Serdar Ceylan, Merve Güner, Merve Hafızoğlu, Didem Karaduman, Cansu Atbas, Ibrahim Ileri, Ayse Dikmeer, Arzu Okyar Baş, Cafer Balcı, Burcu Balam Doğu, Mustafa Cankurtaran, Özcan Erel and Meltem Gülhan Halil

Evaluation of oxidative stress parameters in older patients with urinary incontinence

https://doi.org/10.1515/tjb-2024-0143
Received June 18, 2024; accepted November 8, 2024; published online December 25, 2024

Abstract

Objectives: Urinary incontinence (UI) is defined as any type of involuntary loss of urine. Pathophysiological changes that occur in the urinary system due to aging, especially ischemia, cause functional and structural changes in the urinary system. Oxidative stress is caused by an imbalance between the body's oxidative radicals and antioxidant defense systems. In this study, we aimed to investigate the link between UI and oxidative stress indicators in older people.

Methods: Patients were divided into two groups: the group with incontinence and the group without incontinence. A comprehensive geriatric evaluation was performed on all patients, and they were compared according to serum native thiol, disulfide, and ischemia-modified albumin (IMA) levels.

Results: A total of 145 patients aged 65 years and older were included in the study (44, incontinence; 101, continence). The median age of individuals with UI was 75 (69–83) years. Receiver operating characteristic (ROC) curves were made to determine the cut-off for thiol-disulfide homeostasis and IMA. Disulfide and native thiol divide disulfide values were more significant than other oxidative stress parameters. The area under the curve (AUC) values were 0.65 (95 % CI:0.55–0.74) for disulfide and 0.60 (95 %CI:0.50–0.70) for disulfide divide native thiol (p=0.005, p=0.049, respectively).

Conclusions: Thiol disulfide homeostasis and IMA molecules, which are indicators of oxidative stress, were found to have significantly higher levels of disulfide and disulfide divide native thiol in patients with incontinence. We think it may be important to look at the possible therapeutic benefits of paying attention to the levels of these molecules in relation to the management of UI in older people.

Keywords: urinary incontinence; thiol; oxidative stress; homeostasis; geriatric patient

***Corresponding author: Zeynep Şahiner**, Division of Geriatric Medicine, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, 06230, Altındağ, Ankara, Türkiye, E-mail: zynppyds@hotmail.com. https://orcid.org/0000-0003-1256-4412
Funda Eren, Salim Neşelioğlu and Özcan Erel, Department of Biochemistry, Ankara City Hospital, Ankara, Türkiye. https://orcid.org/0000-0002-8174-8904 (F. Eren). https://orcid.org/0000-0002-0974-5717 (S. Neşelioğlu). https://orcid.org/0000-0002-2996-3236 (Ö. Erel)
Serdar Ceylan, Merve Güner, Merve Hafızoğlu, Didem Karaduman, Cansu Atbas, Ibrahim Ileri, Ayse Dikmeer, Arzu Okyar Baş, Cafer Balcı, Burcu Balam Doğu, Mustafa Cankurtaran and Meltem Gülhan Halil, Division of Geriatric Medicine, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Türkiye. https://orcid.org/0000-0001-5885-4023 (S. Ceylan). https://orcid.org/0000-0002-7417-5415 (M. Güner). https://orcid.org/0000-0002-5401-223X (M. Hafızoğlu). https://orcid.org/0000-0001-5824-8277 (D. Karaduman). https://orcid.org/0000-0001-9990-092X (C. Atbas). https://orcid.org/0000-0002-6164-3603 (I. Ileri). https://orcid.org/0000-0003-3016-8173 (A. Dikmeer). https://orcid.org/0000-0002-1518-5939 (A. Okyar Baş). https://orcid.org/0000-0002-1478-1106 (C. Balcı). https://orcid.org/0000-0002-4430-6146 (B.B. Doğu). https://orcid.org/0000-0002-8213-7515 (M. Cankurtaran). https://orcid.org/0000-0001-7597-8140 (M.G. Halil)

Introduction

Urinary incontinence (UI) is defined as involuntary leakage of urine, regardless of volume [1]. Anatomical and physiological changes in the urinary system that occur with aging, increase in comorbid diseases, cognitive disorders, and medications facilitate the development of UI [2]. Since urinary system disorders cause severe symptoms that affect the quality of life, assessing and understanding the mechanisms behind these disturbances is important for managing and treating them [3]. Age-related lower urinary tract illnesses are associated with ischemia, inflammatory processes, and variations in hormones. Evidence on the role of aging in these disorders is limited, although studies have investigated some pathophysiological mechanisms [4]. Determining the mechanisms and common points of lower urinary tract

disorders may provide insight into pathogenesis and treatments.

Oxidative damage, which results from a discrepancy between the generation of reactive oxygen species (ROS) and the body's total antioxidant capacity (TAC) to counteract their harmful effects, is widely implicated as a critical contributor to the aging process. Over time, the cumulative damage from ROS can accelerate cellular aging and contribute to the emergence of conditions associated with advancing age, highlighting the critical role of oxidative stress in the aging phenomenon [5].

Reactive oxygen species are chemical compounds produced by aerobic cells in response to cellular injury, which can contribute to oxidative damage if the body's antioxidant mechanisms for defense are exhausted. Both enzymatic and non-enzymatic antioxidant systems mitigate the effects of ROS [6]. Thiols, also referred to as the R-SH molecules, are regarded as non-enzymatic antioxidants owing to their containing a group called sulfhydryl (-SH). Thiols make up a significant portion of the body's total antioxidants. Assessing thiol levels in serum provides valuable insight into the body's antioxidant capacity. The constantly changing process known as thiol-disulfide homeostasis (TDH) involves the oxidation of thiol molecules to form disulfide bonds. After that, these disulfide chains are reduced further to thiol molecules [7]. An upset to this equilibrium can lead to a variety of diseases. These include cancer, diabetes mellitus, urolithiasis, and cardiovascular conditions [8]. Ischemia-modified albumin (IMA) is an influenced albumin form that indicates oxidative stress. It occurs due to the albumin's N-terminus injury in situations like hypoxia or persistent inflammation [9]. Furthermore, the inflaming condition brought on by aging, in which ROS plays an important role, is thought to result in architectural and biochemical disruption in the lower urinary tract [10].

Extensive research has recently examined the intricate association between aging and oxidative stress. While the precise mechanisms driving age-related changes in the urinary tract remain elusive, it is imperative to pursue a comprehensive and multidisciplinary approach in conducting investigations. Our primary objective is to elucidate the connection between UI and oxidative stress markers in geriatric outpatients admitted to the university hospital.

Materials and methods

Study population

Among geriatric patients admitted to the outpatient clinic between May 2023 and September 2023, a total of 145 patients aged 65 years and older were included in the study (44 patients with present incontinence and 101 patients with absent incontinence). Comprehensive geriatric assessments (CGA) were conducted on all participants. Demographic information on gender, age, schooling, relationship status, residential place, and person living with was recorded. Geriatric syndromes such as frailty, number of medications, and record of polypharmacy were kept for every patient. Being over 65 years of age, those who consented to participate in the research and had the ability to understand and answer the issues asked were determined as inclusion criteria. Participants who did not agree to provide serum samples for measurement of thiol-disulfide homeostasis parameters and whose BMI was more than 30 kg/m^2 were excluded.

Comprehensive geriatric assessment

The Katz Activities of Daily Living (ADL) and Lawton-Brody Instrumental Activities of Daily Living (IADL) were used to determine the operational status of participants. Katz's ADL test was assessed using a 6-point rating system that involved asking the patient to independently do everyday duties and provide basic assistance. Living (feeding, continence, using the toilet, bathing, transferring, and dressing) and as individualism evolved, likewise did the number of points [11]. The IADL measures the capability of participants' daily complex activities, such as utilizing the phone, going shopping, cooking, maintaining, doing laundry, using prescription drugs, and managing money, and its score is calculated over 8 points [12]. The dietary condition of the participants was evaluated via the Mini-Nutritional Assessment Short Form (MNA-SF). In the MNA-SF test, the patient's BMI in the last three months has seen a decrease in weight, the occurrence of psychological stress or an acute sickness, mobility problems, neurocognitive impairment, and appetite were questioned. In the MNA-SF test, scores >11 points were defined as normal, and 8–11 points were defined as the risk of malnutrition [13]. Handgrip strength (HGS) measurement was used to evaluate muscle strength using the Takei grip strength dynamometer. Measurements were taken three times with the dominant hand in a seated position, with the elbow bent at 90 °, and with the hand in a neutral position. The highest of the three repeated measurements was used in the analyses. The revised EWSGOP sarcopenia criteria were used to determine the cut-off values, and low muscular strength was defined for males and women as HGS<27 kg and HGS<16 kg, respectively [14]. The number of medications was also recorded, and the use of ≥5 medications was considered polypharmacy. The Clinical Frailty Scale (CFS)

was carried out by the same experienced physician to evaluate frailty status. Based on the physician's clinical judgment and a rating that ranges between 1 and 9, CFS describes clinical frailty. Patients were categorized into two groups based on established standards: non-frail/robust (CFS<4) and living with frailty (CFS≥4) [15].

Urinary incontinence assessment

"The complaint of any involuntary leakage of urine in the past 12 months" is the definition of UI [16].

Measurement of oxidative stress parameters

Peripheral venous blood samples taken from the patients after 8 h of fasting were centrifuged (in two biochemistry tubes) at 1,600 *g* for 10 min, then the bloodstream component was divided from the sample and kept cold (−80 °C) pending analysis. Thiol-disulfide homeostasis and IMA tests were performed with the spectrophotometric technique that Erel and Neselioğlu described. After that, formaldehyde was employed to remove any excess reductant in order to stop DTNB (5,5′-dithiobis-2-nitrobenzoic acid) from being reduced after reacting with DTNB; thiol groups were detected and measured [17, 18]. Total thiol groups, including reduced and native thiol groups, were determined after reactions with DTNB. The disulfide parameter value can be calculated as half of the native thiol content and the total thiol content. The disulfide/total thiol, disulfide/native thiol, and native thiol/total thiol ratios were calculated. A colorimetric method described by Bar-Or et al. was used to measure serum IMA concentrations, and the results obtained are included in the text as absorbance units [19]. The albumin test was measured using the spectrophotometric method, while the CRP test was measured based on the turbidimetric method. Both parameters were measured on the Atellica Solutions automated analyzer (Siemens Healthineers, Erlangen, Germany).

Statistical analyses

The statistical analyses were carried out using the SPSS software package, version 23. The variables were evaluated for normal distribution using visual (histograms, probability charts) and analytical (Kolmogorov–Smirnov test) techniques. Descriptive analyses were introduced by using percentages for categorical variables, mean ± standard deviations (SD) for normally distributed variables, and median (min-max) with non-normally distributed quantities. The study employed the Mann-Whitney U test to compare continuous variables and the chi-square test to assess differences between the two types of variables. Every p-value was evaluated against a significance threshold of 5 % using two-sided testing. The relationship between UI and oxidative stress parameters was presented using multivariable binary analysis by logistic regression.

Ethics committee

The Clinical Research and Ethics Committee of Hacettepe University Faculty of Medicine approved the study protocol with ID: 2023/12–20 (GO 23/606) number. Written informed consent was obtained from all participants. The study protocol was in accordance with the Declaration of Helsinki.

Results

The average age of the study population was 72 (68–77) years, and the 60 patients (87 %) were female. The median IMA level of patients without UI was 0.85 (0.67–0.94), the median IMA level of patients with UI was 0.84 (0.69–0.89) (p=0.35), and the levels were similar. The female ratio in patients present and absent UI was 54 % vs. 75 % respectively (p=0.02). Other demographic features were similar in the two groups, except for education level. In patients present UI, the median Katz ADL score was recorded as 5 (5–6), whereas it was 6 (6–6) in those absent UI; this difference exhibited significance in statistics (p<0.001). The ratio of the patients living with frailty evaluated with CFS was considerably greater in patients present UI group than those absent UI (66 % vs. 45 %, respectively, and p=0.02). Furthermore, the median CFS score was 4(3–5) in patients present UI group, and it was 3 (3–4) in those absent UI (p=0.002). Malnutrition was more commonly observed in patients present UI than those absent UI; the malnutrition rate was 41 % (n=18) in patients present UI, whereas only 23 patients (23 %) had malnutrition in those absent UI (p=0.03). The mean HGS with and without UI was 16.4 ± 5.6 kg and 17.1 ± 4.6 kg in female patients (p=0.51), whereas in males, it was 28.6 ± 7.5 kg in those present UI and 22.9 ± 8.7 kg in those absent UI, and the difference was statistically significant (p=0.03). There were no variations between the two groups in terms of multimorbidity and polypharmacy (Table 1).

Oxidative stress markers in patients with and without UI are presented in Table 1. While the disulfide and disulfide/native thiol levels were 14.6 (13.3–16.2) μmol/L, 5 (4.4–5.7) μmol/L in the patients absent UI group, they were 16 (14.4–

Table 1: Baseline characteristics and oxidative stress markers of study population according to groups. The study sample was divided into two groups: the absent incontinence and the present incontinence groups.

Parameters	Total	Incontinence		p-Values
		Absent (n=101)	Present (n=44)	
Age[c], years	72 (68–77)	71 (68–76)	75 (69–83)	0.03
Sex[a] (female)	87 (60)	54 (54)	33 (75)	0.02
Marital status[a] (married)	90 (63)	65 (65)	25 (58)	0.44
Education[a]	107 (74)	69 (68)	38 (86)	0.02
Multimorbidity[a]	125 (86)	86 (85)	39 (89)	0.58
Polypharmacy[a]	74 (51)	49 (49)	25 (57)	0.36
Katz ADL[c]	6 (5–6)	6 (6–6)	5 (5–6)	<0.001
Lawton-Brody IADL[c]	8 (7–8)	8 (7–8)	8 (6–8)	0.04
MNA-SF[c]	13 (11–14)	13 (12–14)	12 (10–14)	0.008
Percentage of patients with MNA-SF score ≤11[a]	41 (28)	23 (23)	18 (41)	0.03
CFS[c]	4 (3–5)	3 (3–4)	4 (3–5)	0.002
Percentage of patients with CFS score ≥4[a]	74 (51)	45 (45)	29 (66)	0.02
Handgrip strength[b], kg				
Female	16.8 ± 5.0	17.1 ± 4.6	16.4 ± 5.6	0.51
Male	27.6 ± 8.0	28.6 ± 7.5	22.9 ± 8.7	0.03
Native thiol[b], µmol/L	299 ± 62	301 ± 65	293 ± 55	0.49
Disulfide[c], µmol/L	15.4 (14.2–17.0)	14.6 (13.3–16.2)	16.0 (14.4–17.9)	0.005
Disülfid/native thiol[c], µmol/L	5.2 (4.6–6.0)	5.0 (4.4–5.7)	5.3 (4.7–6.2)	0.049
IMA[c], µmol/L	0.84 (0.67–0.93)	0.85 (0.67–0.94)	0.84 (0.69–0.89)	0.35
CRP[c], mg/L	0.45 (0.30–0.84)	0.40 (0.30–0.77)	0.50 (0.27–0.90)	0.62
Albumin[c], g/dL	4.2 (4.0–4.4)	4.2 (4.0–4.4)	4.2 (3.9–4.3)	0.17

Variables were presented as n (%)[a], mean±SD[b] or median (min-max)[c]. ADL, activities of daily living; IADL, instrumental activities of daily living; MNA-SF, mini-nutritional assessment short-form; GDS, geriatric depression scale; CFS, clinical frailty scale; IMA, ischemia modified albumin; CRP, C-reactive protein.

17.9) µmol/L and 5.3 (4.7–6.2) µmol/L in the patients present UI group, the differences were statistically significant (p=0.005 for disulfide levels and p=0.049 for disulfide/native thiol ratio, respectively). The other markers were similar in the two groups (p>0.05 for all).

In Table 2, the relationship between UI and oxidative stress parameters is presented according to multivariate binary logistic regression analysis. Disulfide levels were significantly and independently associated with UI (OR: 0.83 and 95 % CI: 0.71–0.97, p=0.02). As the disulfide level increases, the likelihood of UI increases, regardless of other factors. On the other hand, disulfide/native thiol was not associated with incontinence. The OR was calculated as 0.71 for disulfide/native thiol (OR: 0.71, 95 % CI: 0.49–1.04, p=0.08).

In Figure 1, Receiver operating characteristic (ROC) curves were made to determine the cut-off for thiol-disulfide homeostasis and IMA. Disulfide and native thiol divide disulfide values were more significant, and the area under the curve (AUC) values were 0.52 (95 % CI:0.42–0.61) for native thiol, 0.65 (95 % CI:0.55–0.74) for disulfide, 0.60 (95 % CI:0.50–0.70) for disulfide divide native thiol, and 0.55 (95 % CI:0.35–0.45) for IMA (p=0.713, p=0.005, p=0.049, p=0.352, respectively) (Table 3).

Discussion

Oxidative stress is essential in the development and exacerbation of geriatric syndromes, primarily due to its detrimental effects on cellular structures, DNA, and proteins,

Table 2: Results of multivariable binary logistic regression analysis oxidative stress parameters and urinary incontinence (Backward model).

	OR	95 % CI	p-Values
Model 1			
Age, continuous	1.06	0.99–1.13	0.06
Malnutrition	2.47	1.09–5.60	0.03
Disülfid, µmol/L	0.83	0.71–0.97	0.02
Model 2			
Age, continuous	1.08	1.01–1.15	0.02
Sex, male	0.34	0.15–0.80	0.01
Frailty	2.25	1.01–5.00	0.04
Disulfide/native thiol, µmol/L	0.71	0.49–1.04	0.08

OR, odds ratio; CI, confidence interval. Model 1, age (continuous), sex, frailty (CFS≥4), malnutrition (MNA-SF≤11), and disülfid; Model 2, age (continuous), sex, frailty (CFS≥4), malnutrition (MNA-SF≤11), and disülfid/native thiol.

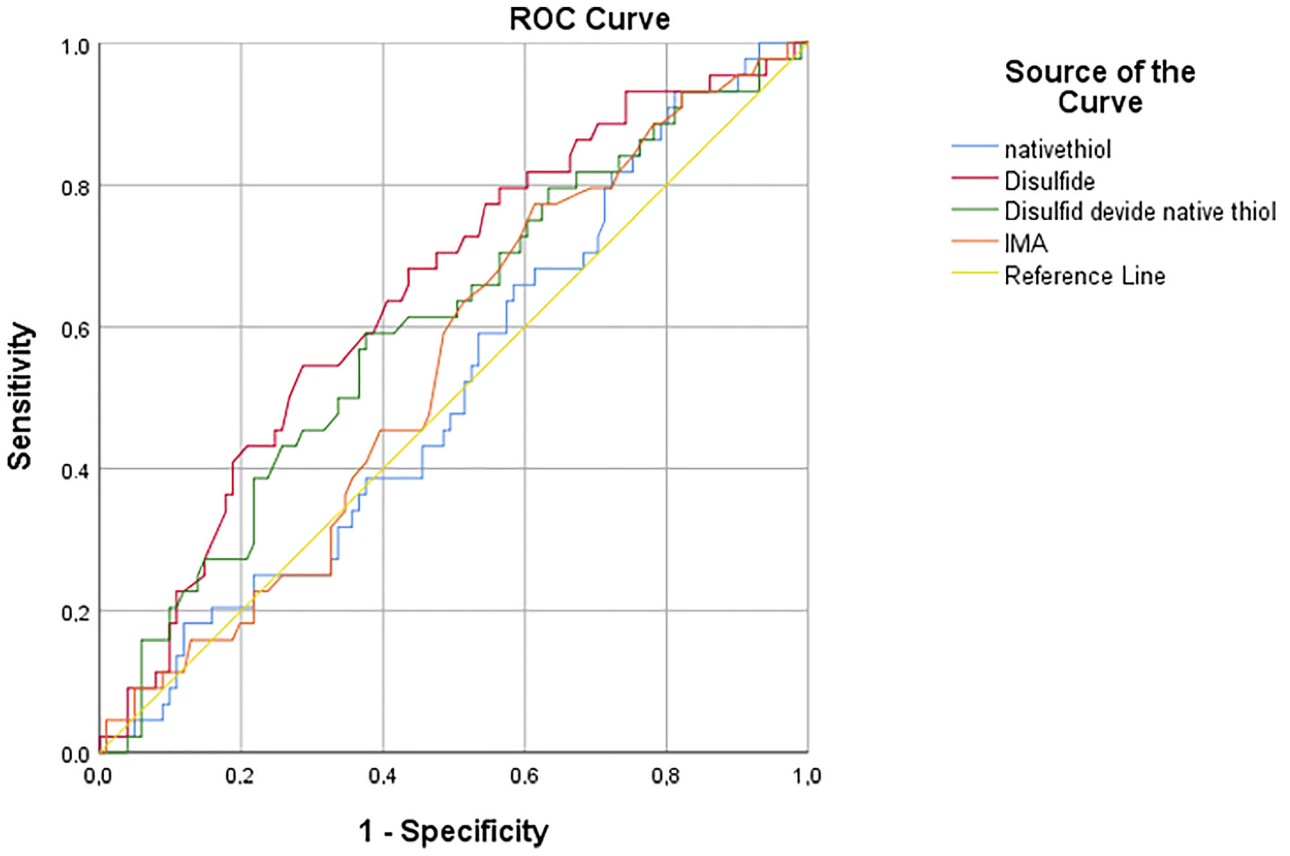

Figure 1: ROC curve analysis of thiol-disulfide homeostasis and IMA for urinary incontinence.

Table 3: ROC analysis of the oxidative stress parameters.

Variables	Cut-off point	AUC	95 % CI	p-Values	Sensitivity, %	Specificity, %
Native thiol	303	0.52	0.42–0.61	0.713	0.47	0.49
Disulfide	15.95	0.65	0.55–0.74	0.005	0.70	0.49
Disülfi divide native thiol	5.25	0.60	0.50–0.70	0.049	0.61	0.50
IMA	0.85	0.55	0.35–0.45	0.352	0.59	0.48

IMA, ischemia-modified albumin; CI, confidence interval; AUC, the area under the curve.

which brings about cumulative harm and failure in various organ systems associated with age-related conditions. In this study, we sought to assess the connection between oxidative stress parameters and UI in community-dwelling older patients. According to our findings, an increase in disulfide levels is associated with an increased likelihood of UI, independent of other influencing factors related to age, gender, nutrition, and frailty status.

A review of the existing literature reveals numerous studies dedicated to investigating the interaction of oxidative stress and the urinary system. It is noteworthy that elevated oxidative stress levels account for a significant proportion of the structural and functional alterations observed within the urinary system. When the generation of ROS and TAC is out of balance, it is referred to as oxidative stress [20]. This imbalance can lead to oxidative damage to cells and tissues. Oxidative stress can lead to the deterioration of muscle cells and tissues; in previous studies, it was shown that markers of oxidative stress and age-related muscle decline were related [21]. Skeletal muscle health plays a critical role in maintaining continence; it was shown that pelvic and abdominal muscles were related to UI. Oxidative damage to these muscles can result in weakened muscle tone and reduced control, potentially contributing to incontinence [22]. Another possible mechanism for oxidative stress and incontinence is that oxidative stress can also affect connective tissues, which offer support to the bladder, urethra, and rectum [20]. Excessive oxidative stress damages

structures, macromolecules, mitochondrial DNA, and tissues through fibrosis [23]. Additionally, this chronic activation activates enzymes and damages DNA; it has been found that this stimulates fibroblast proliferation, leading to structural changes such as detrusor hypertrophy [24]. In a retrospective study, urinary oxidative stress parameters, UI, and bladder pathologies were examined, and as a result, they were found to be significant, similar to our study [24].

Oxidative stress markers and UI may share common risk factors, including lifestyle-related factors. Lifestyle choices such as poor dietary habits, sedentary behavior, and smoking can contribute to both increased oxidative stress levels and the development or exacerbation of UI. Furthermore, Yuan et al. demonstrated a strong inverse relationship between anti-oxidative diet and lifestyle, as represented by oxidative balance score, and the prevalence and severity of UI in females in the United States [25]. Even though we could not evaluate the lifestyle factors in our study, exploring these shared risk factors can provide valuable insights into potential preventive and therapeutic strategies targeting both oxidative stress and UI in affected individuals.

Oxidative stress is frequently linked to chronic inflammation, a condition characterized by prolonged and heightened immune system activity. In the context of UI, chronic inflammation can have a profound effect on the intricate nerve pathways that regulate the coordination of muscles and nerves responsible for maintaining continence [26]. Over time, this sustained inflammation can disrupt the delicate signaling mechanisms between the brain and these vital elements that comprise the urinary system, resulting in a breakdown in the control and coordination required for maintaining continence.

The cumulative effects of oxidative stress and inflammation can thus significantly contribute to the development and progression of UI in affected individuals. Our findings also supported the previous literature stating that oxidative markers are associated with UI. Therefore, it is plausible that the increased disulfide level acts as an oxidative marker that may contribute to the development of UI in affected individuals.

The presence of oxidative stress has been documented in investigations clinics involving different types of lower urinary tract disorders (LUTD) beyond diabetes, as reported in studies by Matsuo et al. [27]. Furthermore, markers of oxidative stress, such as 8-hydroxy-2′-deoxyguanosine, have been suggested as potential biomarkers for lower urinary tract symptoms in a broader context, as indicated in research [28]. Similar to previous studies, we also found that a different oxidative biomarker, disulfide levels, were associated with UI. These findings highlight the potential significance of oxidative stress assessment in understanding and diagnosing UI.

Limitations of this study include its cross-sectional nature and other unmeasured confounding factors, which limit our ability to attribute cause and effect to our observations and create selection bias (related to age, gender, and reliance on self-report measures). The most important of these factors are the confounding limitations of the IMA in its measurement and clinical utility [29]. In diagnosing UI, we evaluated the patients according to their history without further examination. We were unable to address the influence of any dietary factors or medication restrictions prior to serum sampling. In addition, to the best of our knowledge, this is an initial investigation to assess albumin levels altered by ischemia and thiol-disulfide homeostasis in older individuals with incontinence despite the limitations. Although further studies are needed, our findings support the clinical importance of oxidative stress assessment in people with UI.

In our study assessing oxidative stress parameters in individuals aged 65 and above present and absent UI, we observed that native thiol and IMA levels exhibited comparable values between older patients with present and absent UI. Notably, our findings revealed a significant distinction in disulfide levels and the disulfide/native thiol ratio between these two groups, suggesting a potential association between increased disulfide levels and the presence of UI in the geriatric population. For future research, it is critical to investigate the underlying mechanisms and causative factors responsible for this observed relationship, as well as the potential therapeutic implications of targeting disulfide levels in the management of UI in geriatric individuals. Antioxidant approaches to therapy, which are typically difficult to plan, appear to have the potential to improve the quality of life for people suffering from incontinence.

Research ethics: Ethical approval was obtained from the local Institutional Review Board.
Informed consent: Informed consent was obtained from all individuals included in this study.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: Authors state no conflict of interest.
Research funding: None declared.
Data availability: None declared.

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