SCINDEKS Serbian Citation Index
J Med Biochem 2020; 39 (1) DOI: 10.2478/jomb-2019-0003

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 39: 1–6, 2020

Original paper
Originalni naučni rad

VITAMIN D AND THIOL-DISULFIDE HOMEOSTASIS LEVELS IN POST-MENOPAUSAL WOMEN WITH OVERACTIVE BLADDER SYNDROME

VITAMIN D I NIVOI TIOL-DISULFIDNE HOMEOSTAZE KOD ŽENA U POSTMENOPAUZI SA SINDROMOM PREAKTIVNE BEŠIKE

Yasemin Ustundag[1], Iknur Aykurt Karlıbel[2], Murat Sambel[3], Murat Ozturk[3], Atilla Satır[3], Elif Yolgosteren[2], Salim Neselioglu[4], Ozcan Erel[4]

[1]Saglik Bilimleri University, Bursa Yuksek Ihtisas Education and Research Hospital, Department of Clinical Laboratory, Bursa, Turkey
[2]Saglik Bilimleri University, Bursa Yuksek Ihtisas Education and Research Hospital, Department of Physical therapy and Rehabilitation, Bursa, Turkey
[3]Saglik Bilimleri University, Bursa Yuksek Ihtisas Education and Research Hospital, Department of Urology, Bursa, Turkey
[4]Ankara Yildirim Beyazit University, Clinical Biochemistry, Ankara, Turkey

Summary

Background: This study aimed to find a relationship between vitamin D concentration and thiol-disulfide homeostasis in the pathophysiology of overactive bladder (OAB) syndrome in postmenopausal women.
Methods: A total of 76 postmenopausal women, referred for routine controls, were recruited between January and March 2018 to participate in this study. Participants with an overactive bladder questionnaire (OAB-q) score of >11 (n = 34) were included in the OAB syndrome group, while those with a score of <5 (n = 42) were included in the control group. Serum total antioxidant capacity, ischemia-modified albumin, C-reactive protein, 25-hydroxy vitamin D levels, and thiol-disulfide homeostasis were measured.
Results: Patients with OAB syndrome had waist circumferences of 106 ± 11 cm, and their body mass indexes (BMIs) were 30.8 ± 4.8 kg/m^2. The control groups' waist circumferences were 102 ± 11 cm and their BMIs were 28.9 ± 4.3 kg/m^2 (p = 0.069 and p = 0.098, respectively). The level of vitamin D in the control group was 33.7 (IQR: 30.7) nmol/L and 27.0 (IQR: 27.5) nmol/L (p = 0.081) in the OAB syndrome group.

Kratak sadržaj

Uvod: Cilj ove studije je bio da se nađe veza između koncentracije vitamina D i tiol-disulfidne homeostaze u patofiziologiji sindroma preaktivne bešike (OAB) kod žena u postmenopauzi.
Metode: Između januara i marta 2018. godine ukupno je odabrano 76 žena u postmenopauzi da bi učestvovale u ovoj studiji, koje su potom upućene na rutinske kontrole. Učesnice studije koje su imale skor od > 11 (n = 34) na upitniku za preaktivnu bešiku su uključene u grupu sa OAB sindromom, dok su one sa skorom od < 5 (n = 42) uključene u kontrolnu grupu. Izmereni su ukupni antioksidativni kapacitet seruma, albumin modifikovan ishemijom, C-reaktivni protein, 25-hidroksi nivoi vitamina D i tiol-disulfidna homeostaza.
Rezultati: Pacijentkinje sa OAB sindromom su imale obim struka od 106 ± 11 cm, a njihovi indeksi telesne mase (BMI) bili su 30,8 ± 4,8 kg/m^2. Obim struka kontrolne grupe bio je 102 ± 11 cm, a njihovi BMI bili su 28,9 ± 4,3 kg/m^2 (p = 0,069 i p = 0,098, respektivno). Nivo vitamina D u kontrolnoj grupi bio je 33,7 (IQR: 30,7) nmol/L, u grupi sa OAB sindromom 27,0 (IQR: 27,5) nmol/L (p = 0,081).

Address for correspondence:
Yasemin Ustundag
Mimar Sinan Mah. Emniyet Cad. Polis Okulu Kar ısı Yıldırım, Bursa, Turkey
Telephone: +905324823692
e-mail: yaseminbudak2000@yahoo.com

Conclusions: We were not able to demonstrate with certainty any significant relationships between serum 25-hydroxy vitamin D levels and thiol-disulfide homeostasis parameters and OAB syndrome.

Keywords: C-reactive protein, disulfides, postmenopause, urinary bladder, overactive, vitamin D

Zaključak: Nismo bili u mogućnosti da sa sigurnošću dokažemo bilo kakve značajne veze između nivoa 25-hidroksi vitamina D u serumu i parametara tiol-disulfidne homeostaze i OAB sindroma.

Ključne reči: C-reaktivni protein, disulfidi, postmenopauza, mokra na be ika, preaktivna, vitamin D

Introduction

Overactive bladder (OAB) syndrome is a common clinical condition that affects millions of people worldwide. It is defined by urgency, urinary incontinence, and frequency (>8/24 hour) in the absence of metabolic (e.g. diabetes) or local pathological factors (1). Advanced age (>40 years), menopause, parity >2, constipation, and high body mass index (BMI) are risk factors for OAB syndrome (1). Detrusor overactivity and involuntary contractions during the filling phase of the bladder result in decreased functional bladder capacity and associated symptoms (1).

Vitamin D, a fat-soluble prohormone, is biologically inert when derived from diet or elicited in the skin from sunlight, and requires two consecutive hydroxylations in the human body for activation. Vitamin D plays an important role in the human body and its deficiency, related to many health problems, is a global issue (2).

Vitamin D receptors are found in nearly 30 different tissues, including the human bladder (3). The pelvic floor musculature, which provides a constrictor mechanism for the urethra, expresses a vitamin D receptor that plays a significant role in attaining urinary continence (4). It has been suggested that vitamin D deficiency might lead to bladder dysfunction through its effect on the smooth muscles of the detrusor and pelvic musculature (3–5). Higher dietary vitamin D intake has also been shown to lower the risk of OAB syndrome onset (6).

The loss of balance between reactive oxygen species (ROS) and antioxidant defence mechanisms against them is defined as oxidative stress. Vitamin D has been shown to have in vitro anti-oxidant and anti-inflammatory effects, which might link vitamin D deficiency to an increased probability of developing diseases (7, 8). In a recent study, Dokumacioglu et al. (9) showed that the levels of the oxidative stress markers, urinary malondialdehyde and 8-hydroxy-2'-deoxyguanosine, increased in women with OAB syndrome compared with a healthy control group.

Oxidative stress has been shown to contribute to the etiopathogenesis of some diseases, and it can be measured by a new marker, dynamic thiol-disulfide homeostasis (10, 11). This technique is simple and fast, and it can be used in routine laboratory practice to assess and monitor oxidative stress. Alvarez et al. (8) demonstrated that serum 25(OH)D concentrations were independently associated with major plasma thiol/disulfide redox systems, suggesting that vitamin D status may be involved in redox-mediated pathophysiology.

In this study, we aimed to determine the relationship between vitamin D concentration and thiol-disulfide homeostasis, as an oxidative stress marker, in the pathophysiology of OAB syndrome in postmenopausal women.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the research ethics committee. All the subjects gave their written, informed consent, and all the authors followed the ICMJE's requirements for privacy.

Postmenopausal women who had been referred for routine controls (aged 50 or older), recruited between January and March 2018, were invited to participate in the study, and an OAB examination was performed in the urology clinic.

Women with urinary tract infections, urinary stones, infections, or other urinary system pathologies; a history of malignancy; current active malignant neoplasm; cardiovascular disease; chronic neurological, hematologic, infectious, musculoskeletal, psychiatric, or endocrine disease; stress urinary incontinence; those who smoked; take antioxidant drugs or vitamins; or receiving treatment for OAB syndrome were excluded from the study. The participants who were accepted into the study answered an overactive bladder questionnaire (OAB-q) (12). The OAB-q included eight questions about the severity of a patient's complaints that were answered using a 6-point scale, ranging between no (0), very few (1), a little (2), quite a few (3), a lot (4), and too many (5). The total score ranged between 0 and 40.

In our study, those with an OAB-q score of >11 were evaluated as having OAB syndrome. Those with an OAB-q score <5 were included in the control group.

The patients' height, weight, and waist circumference were recorded, and a BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Serum calcium, phosphorus, triglyceride, high-density lipoprotein (HDL), low-

Table I Characteristics of the study population.

Characteristics	Women without OAB	Women with OAB	p
Number of subjects (n)	34	42	
Age (years)	54.0 ± 3.4	54.6 ± 4.5	0.600
OAB-q	1 (2.0)	18 (12.0)	< 0.001
Waist circumference (cm)	102 ± 11	106 ± 11	0.069
BMI (kg/m^2)	28.9 ± 4.3	30.8 ± 4.8	0.098
Waist circumference/height	0.64 ± 0.07	0.67 ± 0.07	0.098
Triglyceride (mmol/L)	1.86 ± 1.12	1.84 ± 1.08	0.927
Total cholesterol (mmol/L)	6.05 ± 1.13	5.58 ±1.08	0.071
HDL (mmol/L)	1.42 ± 0.38	1.42 ± 0.43	0.835
LDL (mmol/L)	3.7 ± 0.98	3.36 ± 1.00	0.089
AIP	0.046 ± 0.26	0.048 ± 0.31	0.982
CRP (nmol/L)	29.5 (0.9)	29.5 (0.9)	0.994
Ca (mmol/L)	2.39(0.07)	2.37(0.12)	0.724
Hba1c (%)	5.9(0.7)	5.8(0.5)	0.363
Vit D (nmol/L)	33.7 (30.7)	27.0(27.5)	0.081
PTH (pmol/L)	6.15 (3.9)	6.68 (4.0)	0.715
FRAP (µmol/L)	1120 ± 264	1135 ± 283	0.842
Alb (g/L)	55 ± 17	46 ± 10	0.151
IMA (AU)	0.569 ± 0.219	0.629 ± 0.257	0.335
Native thiol (µmol/L)	356 ± 73	331 ± 64	0.156
Total thiol (µmol/L)	394 ± 70	365 ± 65	0.095
Disulfide (µmol/L)	19.0 ± 6.2	17.0 ± 4.2	0.118
Disulfide/native thiol	5.1 (1.8)	5.3 (2.8)	0.710
Disulfide/total thiol	4.8 (1.4)	4.8 (2.2)	0.720
Native thiol/total thiol	90.2 (2.9)	90.2 (4.5)	0.725

Data are expressed as mean ± standard deviation when normally distributed, otherwise as median (interquartile range). OAB-q: overactive bladder questionnaire; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; Ca: calcium; Vit D: vitamin D, AIP: atherogenic index of plasma; CRP: C reactive protein; OAB: overactive bladder; IMA: ischemia-modified albumin; FRAP: ferric reducing power of plasma, AU: absorbance unit. *$p < 0.05$ was considered significant for statistical analyses. Mann-Whitney U or student t used for statistical analysis.

density lipoprotein, and total cholesterol were measured using commercially available assay kits with an auto-analyzer (Olympus AU 2700; Beckman Coulter, Germany). HbA1c levels were measured with a HbA1c analyzer (G8; Tosoh Corporation, Tokyo, Japan); parathormone (PTH) and 25-hydroxy vitamin D levels were measured using an immunoassay system (Advia Centaur XP; Siemens Healthcare Diagnostics, USA), and C reactive protein (CRP) was measured with a nephelometer (BN II System; Siemens Healthcare Diagnostics, USA). The atherogenic index of plasma (AIP) was calculated as log (triglyceride/HDL-c). Total antioxidant capacity was measured using the ferric reducing ability of plasma method (FRAP) (13). Reduced cobalt to albumin-binding capacity levels (IMA) were determined according to the method defined by Bar-Or et al. (14). Thiol-disulfide homeostasis was measured by the method developed by Erel (15).

Statistics

Statistical analyses were performed using the SPSS program, Version 15 (SPSS Inc., Chicago, IL, USA). The normality of the continuous variables was analyzed using the Kolmogorov–Smirnov test. The results were expressed as the mean ± the standard deviation (SD) or the median (interquartile range). Normally distributed continuous variables were compared using the independent sample t-test, but the Mann-Whitney U test was used if the distribution was skewed. The relationships among the variables were examined using Spearman's correlation coefficient.

Results

A total of 76 menopausal women were included in the study. The patients, diagnosed with OAB syn-

drome in the urology clinic, were divided into two groups according to their OAB-q scores: those with a score of <5 (n = 34) were included in the healthy control group, and those with a score of >11 (n = 42) were classified as OAB syndrome. Fourteen patients with scores between 5 and 10 were not evaluated.

The age of the patients and the healthy participants were similar at the time of the examination (p = 0.600). Patients with OAB syndrome had waist circumferences of 106 ± 11 cm and BMIs of 30.8 ± 4.8 kg/m^2. The control group had waist circumferences of 102 ± 11 cm and BMIs of 28.9 ± 4.3 kg/m^2 (p = 0.069 and p = 0.098, respectively) (*Table I*).

The level of vitamin D in the control group was 33.7 (IQR: 30.7) nmol/L and 27.0 (IQR: 27.5) nmol/L in the OAB syndrome group (p = 0.081) (*Table I*). However, the correlation between OAB-q and vitamin D using Spearman's correlation was statistically insignificant (r = -0.095, p = 0.418).

The AIP was 0.048 ± 0.31 in women with OAB syndrome and 0.046 ± 0.28 in the control group (p = 0.982).

We found native thiol 356 ± 83 μmol/L vs 331 ± 64 μmol/L (p = 0.444), total thiol 394 ± 70 μmol/L vs 365 ± 67 μmol/L (p = 0.095), and disulfide 19.0 ± 6.2 μmol/L vs 17.0 ± 4.2 μmol/L (p = 0.118) in the control vs the OAB syndrome patients, respectively (*Table I*).

Vitamin D levels showed a weak negative correlation with waist circumference (r = −0.339, p = 0.004), waist circumference to height ratio (r = −0.362, p = 0.002), and BMI (r = −0.68, p = 0.021). AIP correlated with waist circumference (r = 0.823, p < 0.001), waist circumference to height ratio (r = 0.349, p = 0.003), BMI (r = 0.384, p = 0.001), and FRAP (r = 0.345, p = 0.007).

CRP had a weak positive correlation with waist circumference (r = 0.399, p = 0.001), waist circumference to height ratio (r = 0.420, p <0.001), and BMI (r = 0.369, p = 0.01). There was no correlation between the OAB-q score and any of the examined parameters. The thiol-disulfide homeostasis parameters did not correlate with any parameters investigated in the patient group.

Discussion

We found that the postmenopausal patients with OAB syndrome levels of vitamin D were non-significantly low compared to the control group. Supporting our study, low 25-hydroxy vitamin D blood test levels have been suggested as contributing to pelvic floor muscle weakness, which is involved in urinary incontinence and OAB syndrome (16). High-dose vitamin D therapy has been proven to reduce the severity of urinary incontinence in postmenopausal women (17, 18), and in a survey of 5,816 women aged over 40 years, high dietary vitamin D intake was found to reduce the risk of developing OAB syndrome (19). However, some studies did not find an association between lower urinary tract symptoms and vitamin D deficiency (20). Similarly, in a Korean-patient group, low serum vitamin D was not significantly related to female urinary incontinence matched for risk factors such as menopause, number of pregnancies, hypertension, diabetes, and BMI (21).

The vitamin D levels in our study negatively correlated with waist circumference and BMI. Several studies have demonstrated evidence of an association between low plasma concentrations of 25-hydroxy vitamin D and obesity (22). BMI and waist circumference were higher in the OAB syndrome patients. This was consistent with a recent meta-analysis by Zhu et al. (23) that showed that an increase in BMI is a risk factor for OAB syndrome. The exact mechanisms, explaining the link between obesity and OAB syndrome, are not well-known. In the current study, the inflammatory marker CRP was positively correlated with waist circumference, waist circumference to height ratio and BMI. These findings are in agreement with previously published reports (24).

ROS are normal products of aerobic metabolism. However, excess production of ROS is a common feature of various pathophysiological bladder conditions, although its possible role in the physiopathology of bladder dysfunction has still not been clarified (25, 26).

Masuda et al. (27) suggested that oxidative stress might play a role in the development of bladder dysfunction by increasing detrusor muscle contractility and stimulating bladder afferent fibres. With ageing, there seems to be a decrease in antioxidant mechanisms, and ageing increases the sensitivity of detrusor contraction to oxidative damage (28). Some studies have demonstrated that ROS mediate detrusor muscle activity, which provides insight into possible mechanisms (27, 29, 30).

We speculated that the interplay between vitamin D and oxidative stress might affect the severity of OAB syndrome. However, in our study, total antioxidant capacity, measured as FRAP, and thiol-disulfide homeostasis in the OAB syndrome group were similar to those of the control group, and no correlation was found between the severity of the syndrome. No previous study has investigated thiol-disulfide homeostasis in patients with OAB syndrome.

There was no relationship between vitamin D and CRP in our study. Accordingly, Jorde et al. (31) could not find a correlation between 25-hydroxy vitamin D blood test levels and a number of cytokines and inflammation markers. Yiu et al. (32) also demonstrated that vitamin D did not have a signifi-

cant effect on the serum biomarkers of inflammation and oxidative stress. In addition, we could not find an association between FRAP and vitamin D or vitamin D and CRP. This might be explained by the in vivo studies that have demonstrated that active vitamin D in very high concentrations has an immunoregulatory effect (33).

Alvarez et al. (8) showed that in a large cohort of ambulatory adults, the serum 25-hydroxy vitamin D concentration is related to the plasma circulating major thiol-disulfide redox systems; namely plasma glutathione (GSH), cysteine (Cys), and their associated disulfides. However, we found no correlation between vitamin D and thiol-disulfide homeostasis.

Our study involves certain limitation. For instance, the number of participants in both groups was low. Another drawback of the study is that this cross-sectional study was conducted in only one centre and, thus generalizability may be limited.

In conclusion, we were not able to demonstrate with certainty any significant relationships between serum 25-hydroxy vitamin D levels and thiol-disulfide homeostasis parameters and OAB syndrome.

Acknowledgements. This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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Received: November 17, 2018

Accepted: January 29, 2019