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THE USE OF BIOMARKERS IN THE DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER: CAN WE PREDICT THE PATIENTS WHO WILL BE RESISTANT TO TREATMENT?

Hypothesis / aims of study
Overactive bladder (OAB) is a syndrome with a prevalence between 12% and 17% which increases with ageing. Antimuscarinics are the current primary medical treatment of OAB and ramdomized studies showed that they relieve OAB symptoms up to 50-60% (1). Recently, there have been studies focusing mainly on increasing the efficacy without abbreviating the side effects which is the main concern and the reason for discontinuing medical therapy, regarding OAB treatment. Therefore, biomarkers have drawn attention with their potential for selecting the appropriate patients that would mostly benefit from treatment.
Nerge growth factor (NGF) and brain derived neurotrophic factor (BDNF) are proteins which act as retrograde messengers between nerves and target tissues and their levels have been shown to increase in urine in patients with OAB (2,3). The urine levels of these factors have also been shown to correlate with the severity of the disease with decreasing urine levels after treatment that increase again after the cessation of the treatment (2). The main objective of this study is to define new biomarkers that can predict the severity of the disease and detect the patients that would benefit mostly from the treatment. We tried to select and use biomarkers that play a role in different pathophysiological mechanisms such as NGF, BDNF, glycosaminoglycans (GAG) and monocyte chemoattractant protein 1 (MCP-1).

Study design, materials and methods
Patients who have OAB diagnosis with at least one urgency episode were included in the study. A 3-days bladder diary and a validated OAB questionnaire were given to all patients. Patients who had neurogenic bladder, bladder outlet obstruction (BOO), urinary tract infection, stones and bladder tumours and women with stress type urinary incontinence were excluded. All patients had urinary ultrasonography, urinalysis, urine culture, serum creatinine and C-reactive protein (CRP) levels for differential diagnosis of OAB. A total of 45 OAB patients and 45 healthy age-matched controls were included in this study. In OAB group, solifenacin 5 mg daily was used as the standard treatment. Midstream urine samples from “full” bladders were taken before treatment and at first month of the treatment in OAB group and also from the control group. Urine samples were centrifuged 10 min at 5000g and supernatants were preserved at -20°C.
The biochemical measurements were done, by using commercial kits. Urinary BDNF, NGF, GAG and MCP-1 levels were measured by ELISA, according to the manufacturer’s methods. Results were adjusted according to the urinary creatinine (Cre) levels. Chi-square, 2-independent samples t-test and paired t-test were the statistical tests used and a P value less than 5% was considered as significant.

Results
In OAB and treatment groups, 21 (46.7%) male and 24 (53.3%) female were included in the study. The mean ages of the OAB and treatment groups were 49.1 and 43,6 (±10,6), respectively. In OAB group, 29 (64.5% patients had dry OAB and 16 (35.5%) had wet OAB. There were no significant difference for biomarker levels between dry and wet OAB patients (*P*=0,000). BDNF/Cre, NGF/Cre, MCP-1/Cre and GAG/Cre levels were significantly higher in the OAB group when compared to the control group. The levels of these biomarkers significantly decreased after one month solifenacin treatment. The ratio of decrease in biomarker levels were significantly higher in patients who responded to treatment than the patients with resistant OAB. After one month solifenacin treatment, 30 of 45 patients (66.7%) had their OAB symptoms relieved and 15 (%33.3) patients were resistant to solifenacin. The mean biomarker levels before the treatment (basal levels) were shown in Table-1. Although the levels of all biomarkers significantly decreased after 1 month solifenacin treatment (P=0.0001), the levels in treatment sensitive and treatment resistant groups did not differ significantly (P>0.05 for all biomarkers).
Pre-treatment OAB symptom score was significantly higher (24,9 ± 4,9) in resistant patients than the patients who responded well to treatment (21,4 ± 4,7), (P=0.025). After 1 month treatment, OAB scores were 4.3 ± 1.8 and 22.6 ± 4.5 in sensitive and resistant patients, respectively. When treatment sensitive and resistant female patients were compared according to their menopause status, postmenopausal women were more resistant to treatment when compared to premenopausal group (P=0.024). When subgroups of OAB compared, resistance to treatment was higher in wet OAB group (50%) than the dry OAB group (26%), however the difference was not statistically significant (P=0.078).

Interpretation of results
There have been a continuous research to determine the exact patients who would benefit most from the treatment regarding OAB. Previous studies and a meta-analysis showed that the levels of BDNF/Cre and NGF/Cre were significantly higher in OAB patients. The results of our study were consistent with these findings. The levels of MCP-1/Cre and GAG/Cre were also higher in OAB patients which were also consistent with the previous reports. Although several anticholinergics were used as the primary treatment of OAB for many decades, the response rate of these drugs is about 50-60% and discontinuing treatment is frequently seen because of the side effects. The response rate in our study (66.7%) was close to the higher range in the literature.
The decrease in biomarker levels in OAB group after the treatment showed that these substances have a role in the pathophysiology of OAB. Pretreatment OAB symptom score was significantly higher in resistant patients however we could not demonstrate a significant difference in pretreatment biomarker levels between resistant patients and the patients who responded well to the treatment. Biomarkers used in our study also could not differentiate wet and dry OAB patients.

Concluding message

The use of biomarkers in the diagnosis and management of OAB is gaining more importance and becoming more popular in this field. In our study, high pretreatment biomarker levels and the decrease of these after treatment showed that these biomarkers have a role in the pathophysiology of OAB however they could not predict the patients who would benefit from the treatment and in whom antimuscarinics would be useless. Future studies with higher number of patients and different OAB subgroups are needed to investigate the exact role of these biomarkers and others.

Table-1. *Mean biomarker levels before treatment in overactive bladder patients and healthy volunteers*

	Group	**N**	**Mean**	**SD**	***P***
BDNF/Cr (ng/ml)	OAB patients	45	838,04	310,80	0,000
	Healthy volunteers	45	340,18	199,00	
NGF/Cr (pg/ml)	OAB patients	45	1156,54	436,74	0,000
	Healthy volunteers	45	202,88	48,41	
MCP-1/Cr (ng/ml)	OAB patients	45	617,53	299,18	0,000
	Healthy volunteers	45	155,85	79,38	
GAG/Cr (ng/ml)	OAB patients	45	120,08	42,41	0,002
	Healthy volunteers	45	90,86	60,33	

Table-2. *The level of biomarkers before and after treatment in OAB group*

	Before treatment		**After treatment**		**N**	***P***
	Mean	**SD**	**Mean**	**SD**		
BDNF/Kr (ng/ml)	838,04	310,80	362,38	247,69	45	0,000
NGF/Kr (pg/ml)	1 156,54	436,74	537,67	400,42	45	0,000
MCP-1/Kr (ng/ml)	617,53	299,18	263,60	191,31	45	0,000
GAG/Kr (ng/ml)	120,08	42,41	51,14	44,32	45	0,000

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