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URINE CHEMOKINE BIOMARKER PROFILE AND MULTIVARIATE DATA ANALYSIS SUGGESTS LOW- GRADE INFLAMMATION AS UNDERLYING PATHOLOGY OF THE OVERACTIVE BLADDER

Hypothesis / aims of study
The symptoms of overactive bladder (OAB) have a huge prevalence worldwide. It has been suggested from histological studies on OAB patients that low grade inflammatory changes are the key event in the origin of OAB symptoms. We hypothesized that inflammatory changes in bladder can be tracked by increased urine levels of chemokines.

Study design, materials and methods
Mid stream urine specimens was collected from 17 OAB patients aged between 23 to 85 years of either sex. Patients were stratified into wet or dry OAB based on clinical history of urine leak or pad use. The urine from 10 asymptomatic control subjects was also analyzed by a multiplex panel screen of 32 chemokines/cytokines/ growth factors using Luminex xMAP kit available from Millipore. The normalized chemokine concentrations expressed as pg/mg of creatinine Cr were analyzed by univariate and multivariate statistical tools to identify cytokines/chemokines that could independently associate with OAB.

Results
The following cytokines in the urine were either below the detection limit of our assay or were not consistently detected in any group: IL-1β, IL-13, IL-15, GM-CSF and IFN-α. Univariate data analysis found that elevation of 11 inflammatory cytokines was significantly associated with OAB. Linear relationship of cytokines/chemokines consistently found in the urine of OAB patients was evaluated using squared Pearson correlation coefficients and principal component analysis (PCA), which further revealed that age and IL-5 (marker of eosinophil activity) were significant determinants and principal drivers of the variance in the data. The gain in the predictive accuracy of model was explored by stepwise forward variable selection and logistic regression, which demonstrated that odds ratio OR for having OAB increased by 57% for every unit increase of IL-5 levels relative to controls. Furthermore, the 16% increase in OR for getting OAB for each additional year of age in patients highlighted the higher prevalence of OAB in elderly population. Multivariable OR (95% CIs) and p values for these two variables are summarized below:

	OR	95% CI	p value
Age	1.1618	(0.9812, 1.3755)	0.08
IL-5	1.5682	(1.0118, 2.4306)	0.0442

Interpretation of results
The base OAB predictive model used data from univariate and multivariate modeling incorporating information about patient age, gender and levels of urinary cytokines. A pattern consistent with previous reports of allergic inflammation underlying OAB pathogenesis was revealed by the linear combination of elevated cytokines leading to the selection of IL-5 as independent predictor of OAB. IL-5 is responsible for chemotaxis of eosinophils and it has been previously been associated with allergic inflammation of asthma. Elevation of sIL-2Rα suggests compensatory response to elevation of pro-inflammatory chemokines/ cytokines in OAB. Urine levels of these chemokines are expected to decrease in patients well managed by therapy.

Concluding message
Urine chemokines may be an objective non-invasive biomarker for OAB and predictor of response to therapy and disease progression.

References
1. Loran et al. Allergic inflammation as one of the factors of pathogenesis of overactive urinary bladder. Urologiia: 37, 2007

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Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**