SYSTEMATIC REVIEW

Brain-derived neurotrophic factor, nerve growth factor, and high sensitivity C-reactive protein levels in urine in overactive bladder patients: a meta-analysis [version 1; peer review: 2 not approved]

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Abstract

Background: Overactive bladder (OAB) is a clinical syndrome characterized by a combination of symptoms including urgency, frequency, and nocturia, with or without urinary incontinence. Overactive bladder has a high prevalence especially in those of an older age and women, with diagnosis depending on the patient's symptoms. This study aims to assess brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and high sensitivity C-reactive protein (HSCRP) in urine as biomarkers in OAB.

Methods: Studies were searched from Pubmed, Science Direct, Wiley Online Library, and Google Scholar. All studies assessing BDNF, NGF, and HSCRP in urine in OAB patients were included. The standardized mean difference (SMD) and 95% confidence intervals (CI) were then calculated.

Results: A total of 85 studies were included with a total of 11,483 subjects (6,885 OAB patients and 4,598 controls). Based on data analysis results, urinary NGF/Creatinine (NGF/Cr) and NGF level in OAB patients were significantly higher than control (SMD = 1.00, 95%CI = 0.80-1.20, P<0.00001; and SMD = 1.11, 95%CI = 0.79-1.43, P<0.00001). NGF/Cr level was found higher in OAB with incontinence (OAB wet) compared with OAB without incontinence (OAB dry) (SMD = 0.41, 95%CI = 0.23-0.60, P<0.0001), and decreased after treatment (SMD = 0.76, 95%CI = 0.49-1.03, P<0.00001). Urinary BDNF/Cr level was significantly higher in OAB patients compared with controls (SMD = 1.97, 95%CI = 1.14-2.79, P<0.00001), and also decreased significantly

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after treatment (SMD = 0.75, 95%CI = 0.42-1.08, $P < 0.00001$). The level of HSCRP was significantly higher in OAB patients when compared with controls (SMD = 0.38, 95%CI = 0.12-0.64, $P < 0.004$).

Conclusions: The level of BDNF/Cr, NGF/Cr, NGF, and HSCRP in urine were found higher in OAB compared with controls, which means they may be used as a biomarkers for OAB.

Keywords

brain-derived neurotrophic factor, nerve growth factor, high sensitivity C-reactive protein, overactive bladder

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Introduction

Overactive bladder (OAB) is defined by the International Continence Society as a syndrome characterized with symptoms such as urgency, frequency, and nocturia, with or without urinary incontinence.¹ OAB can affect daily activities and social functions such as work, physical activity, and sleep. OAB prevalence was found to be higher in older patients and women.¹⁻³ Chronic low-grade inflammation is related to old age, which is a risk factor for various morbidities and mortality.⁴ The pro-inflammatory state in aging is believed to cause molecular and structural damage contributing to bladder aging and OAB.⁵ In women, menopause is associated with increased OAB symptoms due to decreased levels of oestrogen after menopause, which has an important role in lower urinary tract function.⁶

OAB diagnosis currently depends on the patient's clinical symptoms rather than molecular identification from samples, such as urine, blood, or other biological samples, which are easy to acquire and analyse. While patient examination includes urodynamic test, symptom questionnaire, and urination diary, which has low objectivity and accuracy.^{7,8}

Brain-derived neurotrophic factor (BDNF), along with nerve growth factor (NGF), is a neurotrophic factor, which is a group of proteins with functions in neuron growth, survival, and differentiation. Neurotrophins are able to bind and activate high-affinity tropomyosin-receptor kinase receptor and low-affinity p75 neurotrophin receptor (p75NTR). Increases of NGF levels have been found in inflammation, while BDNF secretion is induced by NGF in inflamed tissue. NGF also plays a role as a peripheral mediator in inflammation.^{9,10} High sensitivity C-reactive protein (HSCRP) able to detect CRP levels with sensitivity range of 0.01 to 10 mg/L, and HSCRP levels can help to measure low-grade systemic inflammation.¹¹ We perform meta-analysis to assess NGF, BDNF, and HSCRP levels in OAB patients based on previous studies.

Methods

Eligibility criteria and information sources

This study was a meta-analysis study. Inclusion criteria were as follows: studies with OAB patients; studies which measured BDNF, NGF, and HSCRP levels in urine; studies that had data available for size effect analysis (mean, standard deviation, and sample size); and studies available in Bahasa Indonesia or English. Exclusion criteria were review articles, studies in animals, and studies in children. Studies in children were excluded because OAB prevalence was found higher in older patients.

Literature was searched using Pubmed, Science Direct, Wiley Online Library, and Google Scholar. Keywords used for literature searching were ((BDNF OR NGF) OR HSCRP) AND overactive bladder. Information sources were searched until 31 November 2020.

Data collection

The literature searching and data extraction were performed by at least two reviewers independently.

Data variables that were extracted from study samples were as follows: first author name; year of publication; sample size; and BDNF/Creatinine (BDNF/Cr), NGF/Creatinine (NGF/Cr), and HSCRP levels in urine. BDNF/Cr, NGF/Cr and HSCRP levels were extracted in mean and standard deviation.

Data analysis

Data were analysed using standardized mean difference (SMD) and 95% confidence interval (CI) using Review Manager 5.3 software. A P value of less than 0.05 indicated significant statistical data. Heterogeneity was estimated using I^2 and Q test. I^2 above 50% and P value less than 0.05 indicated significant heterogeneity between studies. If I^2 was more than 50%, a random effects model was used. If I^2 was less than 50%, a fixed effects model was used instead.

Publication bias was evaluated using funnel plot.

Results

A total of 85 studies^{7,12-95} were included, with 11,483 subjects (6,885 OAB and 4,598 without OAB) from 969 studies searched from Pubmed, Science Direct, Wiley Online Library, and Google Scholar. Literature searching results can be seen in [Figure 1](#).

Comparison of NGF/Cr levels between OAB patients and controls

Based on data analysis results, NGF/Cr levels in urine was found significantly higher in OAB patients compared to controls (SMD = 1.00, 95% CI = 0.80-1.20, $P < 0.00001$). The heterogeneity test showed significant heterogeneity

Figure 1. PRISMA flowchart.

($P < 0.00001$, $I^2 = 89\%$), so a random effects model was used to analyse data. The results of the forest plot can be seen in Figure 2.

Comparison of urinary NGF levels between OAB patients and controls

Urinary NGF levels were found significantly higher in OAB patients when compared with controls (SMD = 1.11, 95% CI = 0.79-1.43, $P < 0.00001$). Heterogeneity was found ($P < 0.00001$, $I^2 = 91\%$); therefore, a random effects model was used to analyse data. The results of the forest plot can be seen in Figure 3.

Comparison of BDNF/Cr levels between OAB patients and controls

OAB patients have significantly higher levels of BDNF/Cr compared to controls (SMD = 1.97, 95% CI = 1.14-2.79, $P < 0.00001$). Heterogeneity was found ($P < 0.00001$, $I^2 = 97\%$), and a random effects model was used to analyse data. The results of the forest plot can be seen in Figure 4.

Figure 2. Forest plot of NGF/Cr levels comparison between OAB patients and controls.

Comparison of HSCRP levels between OAB patients and controls

HSCRP levels were found to be higher in OAB patients compared with controls (SMD = 0.38, 95% CI = 0.12-0.64, $P < 0.004$). There was significant heterogeneity ($P < 0.00001$; $I^2 = 93\%$), so a random effects model was used in data analysis. The results of the forest plot can be seen in [Figure 5](#).

Comparison of NGF/Cr levels between OAB wet patients and OAB dry patients

Levels of NGF/Cr were found significantly higher in patients with OAB with incontinence (OAB wet) compared with OAB without incontinence (OAB dry) (SMD = 0.41, 95% CI = 0.23-0.60, $P < 0.0001$). A random effects model was used in data analysis because there was a significant heterogeneity ($P < 0.02$; $I^2 = 50\%$). The results of the forest plot can be seen in [Figure 6](#).

Differences in NGF/Cr levels in OAB patients before and after treatment

NGF/Cr levels in urine in OAB patients were significantly decreased after treatment (SMD = 0.76, 95% CI = 0.49-1.03, $P < 0.00001$). Heterogeneity was found ($P < 0.00001$; $I^2 = 88\%$), and a random effects model was used to analyse the data. The results of the forest plot can be seen in [Figure 7](#).

Figure 3. Forest plot of urinary NGF levels comparison between OAB patients and controls.

Figure 4. Forest plot of BDNF/Cr levels comparison between OAB patients and controls.

Figure 5. Forest plot of HSCRP levels comparison between OAB patients and controls.

Figure 6. Forest plot of NGF/Cr levels comparison between OAB wet patients and OAB dry patients.

Figure 7. Forest plot of NGF/Cr levels in OAB patients before and after treatment.

Figure 8. Forest plot of BDNF/Cr levels in OAB patients before and after treatment.

Differences in BDNF/Cr levels in OAB patients before and after treatment

The levels of BDNF/Cr in OAB patients' urine were significantly decreased after treatment (SMD = 0.75, 95% CI = 0.42-1.08, $P < 0.00001$). A random effects model was used in data analysis because significant heterogeneity was found ($P < 0.00001$; $I^2 = 80\%$). The results of the forest plot can be seen in Figure 8.

Subgroup analysis

Subgroup analysis was performed based on subject gender and age. Based on subgroup analysis results, there was a significant difference of NGF/Cr levels in urine in both male (SMD = 0.88, 95% CI = 0.60-1.17, $P < 0.00001$) and female groups (SMD = 1.06, 95% CI = 0.70-1.42, $P < 0.00001$) compared with controls. A significant difference of NGF/Cr levels was also found in the >50 year old (SMD = 0.91, 95% CI = 0.71-1.11, $P < 0.00001$) and the <50 year old groups (SMD = 1.47, 95% CI = 0.77-2.18, $P < 0.00001$) compared with controls.

There was a significant difference of BDNF/Cr levels in urine in both the male (SMD = 1.78, 95% CI = 0.95-2.61, $P < 0.0001$) and female groups (SMD = 2.11, 95% CI = 0.63-3.59, $P = 0.005$). A significant difference was also significantly in both the >50 year old (SMD = 2.35, 95% CI = 0.89-3.80, $P = 0.002$) and the <50 year old groups (SMD = 1.46, 95% CI = 0.95-1.96, $P < 0.00001$).

There was also a significant difference of HSCRP levels in both the male (SMD = 0.63, 95% CI = 0.12-1.13, $P = 0.01$) and female groups (SMD = 0.24, 95% CI = 0.14-0.33, $P < 0.00001$). A significant difference was also found in both the >50 year old (SMD = 0.48, 95% CI = 0.11-0.84, $P = 0.01$) and <50 year old groups (SMD = 0.24, 95% CI = 0.13-0.35, $P < 0.0001$). Subgroup analysis results can also be seen in [Table 1](#).

Publication bias

There was no publication bias by funnel plot ([Figure 9](#)).

Table 1. Subgroup analysis of NGF/Cr, BDNF, and HSCRP levels between OAB patients and controls.

Subgroups	Total studies	Sample size		SMD (95% CI)	P	Heterogeneity	
		OAB	Control			I ² (%)	P
NGF/Cr Levels							
Gender							
Male	2	108	96	1.01 ((-0.83)-2.86)	0.28	95	<0.00001
Female	21	1378	743	1.06 (0.70-1.42)	<0.00001	92	<0.00001
Male and Female	33	1526	1050	0.88 (0.60-1.17)	<0.00001	89	<0.00001
Age							
>50	47	2738	1574	0.91 (0.71-1.11)	<0.00001	86	<0.00001
<50	9	374	305	1,47 (0.77-2.18)	<0.0001	93	<0.00001
BDNF/Cr Levels							
Gender							
Male	0	0	0	NA	NA	NA	NA
Female	10	578	294	2.11 (0.63-3.59)	0.005	98	<0.00001
Male and Female	10	311	331	1.78 (0.95-2.61)	<0.0001	95	<0.00001
Age							
>50	12	587	330	2.35 (0.89-3.80)	0.002	98	<0.00001
<50	8	302	295	1.46 (0.95-1.96)	<0.00001	86	<0.00001
HSCRP Levels							
Gender							
Male	2	1189	762	0.24 (0.14-0.33)	<0.00001	0	0.87
Female	0	0	0	NA	NA	NA	NA
Male and Female	3	1448	1617	0.63 (0.12-1.13)	0.01	96	<0.00001
Age							
>50	4	1609	1955	0.48 (0.11-0.84)	0.010	95	<0.00001
<50	1	1028	424	0.24 (0.13-0.35)	<0.0001	93	<0.00001

Note: Significance level is $P < 0.05$.

Abbreviations: OAB, Overactive Bladder; SMD, Standardized Mean Difference; CI, Confidence Interval; NGF/Cr, Nerve Growth Factor/Creatinine; BDNF/Cr, Brain Derived Neurotrophic Factor; HSCRP, High Sensitivity C-Reactive Protein.

Figure 9. Funnel plot showing publication bias.

Discussions

Based on our analysis, NGF/Cr and NGF levels in urine were found higher significantly in OAB patients compared with controls. Higher NGF/Cr levels were also found in OAB wet patients compared with OAB dry patients. This result is related to higher detrusor muscle activity in OAB wet patients compared with OAB dry.^{96,97} NGF/Cr levels were decreased after various treatments, such as lifestyle management and antimuscarinic. This means NGF/Cr levels could be used to assess therapeutic effects of OAB treatment. An increase of NGF levels occurs in inflammatory conditions or organ dysfunction which has a role in regulation of sensory sensitivity. NGF could sensitise C afferent fibres, which cause urgency and hyperactivation of bladder reflex, resulting in frequency and urgency incontinence.^{98,99} When a cut-off point of 26.32 pg/mg was used, NGF/Cr has a sensitivity and specificity of 93.3% and 64.0%.⁷

In our study, BDNF/Cr levels in urine was found significantly higher in OAB patients compared with controls. An increase of BDNF levels is induced by increased NGF synthesis in inflamed tissue.⁹ Our study showed that BDNF/Cr levels decreased after various treatments, so BDNF/Cr levels could be used to assess therapeutic effect of OAB treatment. Previous research by Antunes-Lopes *et al* in 2013¹⁸ showed that BDNF/Cr levels were higher in OAB patients compared with controls (628.1 ± 590.5 vs 110.4 ± 159.5 ; $P < 0.001$), and the levels decreased after treatment with lifestyle modification (432.5 ± 598.0 ; $P < 0.033$) or treatment with antimuscarinic (146.6 ± 264.9 ; $P < 0.001$).

Based on our data analysis, HSCRP levels was found significantly higher in OAB patients compared with controls. This result shows a connection between inflammation and OAB. Previous research by Kupelian *et al* in 2012¹⁰⁰ showed an association between increases in CRP levels and OAB in males and females. OAB prevalence was also increased with higher CRP levels in that study. An increase in CRP levels could trigger endothelial dysfunction and atherosclerosis. Ischemia caused by atherosclerosis could lead to bladder dysfunction.¹⁰¹ This inflammation and bladder dysfunction then causes the release of various inflammatory mediators, such as NGF and BDNF, which cause an increase in afferent nerve activities resulting in OAB symptoms.¹⁰²

The limitation of our study is the significant heterogeneity on our analysis. This could be caused by variations in methods and populations of included studies.

In conclusion, urinary NGF/Cr, BDNF/Cr, and HSCRP may be used as biomarker in OAB diagnosis and to assess therapeutic effects of OAB treatments. However, there are still low number of HSCRP studies. More studies on these biomarkers and HSCRP assessment in OAB should be performed in the future.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Open Science Framework: PRISMA checklist for 'Brain-derived neurotrophic factor, nerve growth factor, and high sensitivity C-reactive protein levels in urine in overactive bladder patients: a meta-analysis', <https://doi.org/10.17605/OSF.IO/R9XAK>.¹⁰³

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Volkan Sen

Dokuz Eylul University School of Medicine, İzmir, Turkey

The authors evaluated some inflammatory factor levels in urine in overactive bladder patients. I have some concerns about the manuscript;

- Authors must take a PROSPERO number for meta-analysis before the study.
- Which guideline was used for meta-analysis? Authors must state this information and explain step by step
- Authors cannot conclude that 'these factors can be used as a biomarker for OAB.'

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

No

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Urology

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 24 August 2021

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Pradeep Tyagi

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The authors have performed a meta-analysis of reports on urine analysis of NGF, BDNF, and CRP.

The following concerns were noted:

- Authors should cite PMID: 28102552¹ and discuss how their findings reconcile with earlier meta-analyses.
- Authors should discuss the limitation of studies that used the enzyme-linked immunosorbent assay (ELISA), the Promega NGF Emax Immunoassay, to quantify NGF in urine. There have been concerns with the specificity of the assay for NGF as it may have contributed to some false-positive findings due to cross-reactivity with other urinary components, such as immunoglobulin G. Kit was withdrawn from the market in 2014².
- Also, the authors should discuss the rationale for creatinine normalization of neurotrophins (NGF and BDNF) secreted by the bladder of OAB patients into the urine. Do urine levels of NGF or BDNF increase or decrease with the increase in urine creatinine concentration?
- Has anybody reported a correlation or regression coefficient between urine levels of NGF/BDNF and urine levels of creatinine to justify creatinine normalization? It appears the urology community just copied the use of creatinine normalization for NGF and BDNF in OAB for systemic diseases without any proper scientific justification.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Urine biomarkers and pathology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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