CORRELATION BETWEEN LEVELS OF HIGH SENSITIVITY C-REACTIVE PROTEIN (hs-CRP) AND BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) IN THE URINE OF MENOPAUSAL WOMEN WHO EXPERIENCED OVERACTIVE BLADDER AND DID NOT EXPERIENCE OVERACTIVE BLADDER AT H.ADAM MALIK GENERAL HOSPITAL MEDAN

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Abstract

This research is expected to be able to assess the correlation between levels of High Sensitivity C-reactive protein (hs-CRP) and brain-derived neurotrophic factor (BDNF) in the urine of postmenopausal women who experience overactive bladder and do not experience overactive bladder at Adam Malik General Hospital Medan. An observational analytic reserach with case control design in menopausal paramedic women who experienced overactive bladder and did not experience overactive bladder at H Adam Malik General Hospital Medan in January 2019. The research sample was taken by non-probability method with consecutive sampling technique. If the data is normally distributed, the Pearson correlation test is used and if the data are not normally distributed, the Spearman correlation test is used. Hs-CRP level in OAB patients was >1,04 mg/L in 38 patients (100%), and in non OAB patient, hs-CRP level was < 1,04 mg/L in 37 patient (97,3%) with p value = 0,001. BDNF level in OAB patient was > 305,5 pg/L in 38 patients (100%) and in non OAB patient was > 305,5 pg/L in 38 patients (100%). Correlation between hs-CRP and BDNF in patients with OAB with r = 0.525 and p <0.001 while in patients without OAB, r = 0.128 and p = 0.442 (p <0.001). This research shows a significant correlation where hs-CRP levels rise, BDNF will also increase in OAB patients. but there is no correlation between hs-CRP and BDNF in patients without OAB.

Keywords: High Sensitivity C-reactive protein (hs-CRP), brain-derived neurotrophic factor (BDNF), overactive bladder, menopause

I. INTRODUCTION

WHO defines menopause as a period or phase of cessation of the menstrual cycle forever for a woman who has previously menstruated due to cessation of ovarian follicular activity. There was no menstruation for 12 consecutive months because ovary had failed to produce estrogen. According to research conducted by Rusda M in 2014 about menopausal women, menopausal symptoms such as: Hot flushes (15.8%), night sweats (21.8%), palpitations (30.5%), vertigo (30.2 %), restlessness (27.6%), quick temper (39.5%), headache (43.7%), insomnia 37.8%), Depression (24.7%), easily fatigued (37.4 %), muscle pain (28.9%), Impotence (34.6%), vaginal dryness (12.0%), difficulty concentrating (8%), decreased memory (2.2%), arousal sexually reduced (36.5%), and weight gain (25.3%).[1,2]

CRP is one of the acute phase proteins, including a group of proteins in which blood levels increase in acute infections as a nonspecific immune system, form complexes and activate classical pathway complement. CRP measurements are useful for assessing inflammatory disease activity. In study by Hsiao et al found that the median CRP level appeared to be significantly higher in women with OAB compared to women with bladder hypersensitivity (0.12 vs 0.075 mg / dL, p = 0.008) and the control group (0.12 vs 0.055 mg / dL, p = 0.032) suggest a positive correlation between CRP levels and symptom severity. It has also been shown that 1-3 mg / L CRP levels are followed by an increased risk of OAB symptoms which suggest that the inflammatory process plays an important role in the etiopathogenesis of OAB. [3,4,5]

Brain derived neurotrophic factor (BDNF) is a trophic protein derived from tissue that is found in the central nervous system. There is evidence that BDNF plays an important role in the inflammatory process and pain including inflammation in the bladder. Patients with overactive bladder were found to have very high urinary BDNF levels and correlate with symptoms severity of overactive bladder. It has been shown that BDNF / creatinine levels were significantly higher in patients with OAB compared to healthy individuals (980.3 ± 1774.8 vs 110.4 ± 159.5). Measuring BDNF levels can be an acute biological marker for the efficacy of OAB treatment. [6,7]

II. RESEARCH METHODOLOGY

This research was an observational analytic study with a case control design to assess the correlation between the levels of High Sensitivity C-reactive protein (hs-CRP) and Brain-Derived Neurotrophic Factor (BDNF) in urine of menopausal women who experienced overactive bladder and did not experience overactive bladder. This research was conducted at H Adam Malik General Hospital Medan in January 2019 on 38 menopausal paramedic women who experienced overactive bladder and did not experience overactive bladder.

Research samples that met the inclusion criteria which is willing to take part in this research and sign informed consent, women who did not menstruate for 12 consecutive months and were diagnosed with overactive bladder and did not experience overactive bladder based on anamnesis with the OAB score questionnaire, did not take hormone replacement therapy, did not obese, did not suffer from diabetes mellitus, did not suffer from urinary tract infections, did not smoke, did not consume alcohol, did not take antidepressant drugs and are not included in the exclusion criteria which is damaged urine samples, withdraw from research. Samples were taken with non-probability methods with consecutive sampling techniques.

Work Arrangement

After obtaining approval from the Ethics Committee of the Medical Faculty, University of North Sumatra, sampling was taken at H Adam Malik General Hospital in Medan. Samples that met the inclusion and exclusion criteria were given informed consent. Then anamnesis is performed and determines the degree of OAB with the OAB score. Then urine is collected as much as 1 pot of urine to further measurement of hs-CRP and BDNF levels in the laboratory.

Statistical Analyzed

The characteristics of the research sample were analyzed using descriptive statistics for calculating the characteristics of data samples. To see the correlation between hs-CRP levels and BDNF in urine of menopausal women who experienced overactive bladder, firstly a normality test was performed. If the data are normally distributed, the Pearson correlation test is used and if the data is not normally distributed, the Spearman correlation test is used. To facilitate statistical calculation, the researcher uses statistical software SPSS version 20.

III. RESULTS AND DISCUSSIONS

Tabel 1. Distribution of Research Subjects by Age, Parity, Body Mass Index, Duration of Menopause in H. Adam Malik Hospital Medan

Characteristics	OAB		Without OAB	
	N	Percentage	N	Percentage
Age				
45-50 y.o.	5	13,2	4	10,5
51-55 y.o.	33	86,8	34	89,5
Menopause Duration				
2 years	14	36,8	25	65,8
3 years	11	28,9	11	28,9
≥ 4 years	13	34,2	2	5,3
Parity				
Nullipara	0	0	0	0
Primipara	2	5,3	2	5,3
Multipara	30	78,9	33	86,8
Grandemultipara	6	15,8	3	7,9
BMI				
Underweight	0	0	0	0
Normoweight	8	18,2	16	42,1
Overweight	30	68,2	22	57,9
Obesity	0	0	0	0
Degree of OAB				
Mild	20	52,6		
Moderate	13	34,2		
Severe	5	13,2		
Total	38	100	38	100

Table 2. The level of *hs-CRP* in urine of postmenopausal women who experienced OAB and did not experience OAB

		OAB		Non OAB		P Value
		N	%	N	%	
Hs-CRP	**<1.04**	**0**	**0**	**37**	**97.3**	**0.001**
(mg/L)	**>1.04**	**38**	**100**	**1**	**2.7**	
Mean ± SD		**1,33 ± 0,23**		**0,66 ± 0,34**		

From this research it was found that all patients with 100% OAB had a hs-CRP level of ≥ 1.04 while in the non-OAB group there were 37 samples (97.3%) with hs-CRP levels <1.04 and 1 sample (2.7%) with hs-CRP levels ≥ 1.04. In statistical analysis found a p value <0.005, which indicates that in the group with OAB, the level of hs-CRP was higher when compared with the levels of hs-CRP in samples that did not suffer from OAB.

Table 3. The urine BDNF level of menopausal women who experienced OAB and did not experience OAB

		OAB		Non OAB		P Value
		N	%	N	%	
BDNF	**<305.5**	**0**	**0**	**0**	**100**	**0.001**
(pg/L)	**>305.5**	**38**	**100**	**38**	**0**	
Mean ± SD		**430,87 ± 73,58**		**230,97 ± 29,88**		

In this research, it was found that 38 samples with OAB (100%) had BDNF levels ≥ 305.5 while in the control group, 38 samples (100%) had BDNF levels <305.5 with a P value = 0.001, indicating that there was a significant relationship between increasing BDNF and OAB.

Tabel 4. Correlation of urine hs-CRP and BDNF levels of menopausal women who experienced OAB and did not experience OAB at H. Adam Malik Hospital Medan

	r value	p-value
Correlation of urine hs-CRP and BDNF levels of menopausal women who experienced OAB	**0.525**	**0.001**
Correlation of urine hs-CRP and BDNF levels of menopausal women who didn't experienced OAB	**0.128**	**0.0442**

From table 3., the correlation between hs-CRP and BDNF in patients with OAB, there was a moderate positive correlation with r = 0.525 and p <0.001. This shows a significant correlation where hs-CRP levels rise, BDNF will also increase in OAB patients. While the correlation between hs-CRP and BDNF in non OAB subjects with r = 0.128 and p = 0.442 (p> 0.001), this indicates that there is no significant correlation between hs-CRP and BDNF in non-OAB patients

The level of hs-CRP in urine of postmenopausal women who experienced OAB and did not experience OAB at RSUP H Adam Malik Medan

This is in line with the research conducted by Kupelian et al., 2012, it appears that the prevalence of OAB appears to increase with higher hs-CRP levels. The prevalence of OAB symptoms increases with hs-CRP levels> 1 mg / L. Increased hs-CRP > 3 mg / L correlates with a doubling in the odds ratio of OAB. It has also been proven from the research of Tomaszweski, et al., that 1-3 mg / L hs-CRP levels were followed by an increased risk of OAB symptoms suggesting that the inflammatory process plays an important role in etiopathogenesis of OAB.[5,8]

In contrast to research conducted by Chuang YC, et al in 2010 about hs-CRP levels in patients with LUTS, higher levels of 0.15 mg / L were found in only one person with cystitis.[9] In the Chuang et al 2014 study, it was found that serum hs-CRP levels were higher in OAB patients with an average value of 1.83 ± 2.30 mg / L compared to the control group 0.59 ± 0.40 mg / L. Serum hs-CRP values in the study were more or less the same as this research obtained in urine as well as in the control group.[7]

The urine BDNF level of menopausal women who experienced OAB and did not experience OAB at H Adam Malik General Hospital Medan

This is in line with the research conducted by Kashyap, 2017 in a study of the overexpression of BDNF as a mediator of neuronal changes that trigger the onset of OAB. In this study they took bladder tissue from BDNF-injected mice and found an increasement of BDNF protein (45.90 ± 23.60 pg / mg vs. 7.33 ± 3.81 pg / mg) in bladder tissue which is increased significantly (P <0.0013) compared to the group who received luciferase without any changes in NGF. Urine taken a day before tissue retrieval also showed a significant increase in BDNF ((442.20 ± 78.25 pg / mL vs. 120.30 ± 78.86 pg / mL; P <0.0001)) when compared to the luciferase group.[10]

A similar study was also conducted by Lopes, 2013. In patients with OAB the ratio of nerve growth factor to creatinine (488.5 ± 591.8 vs 188.3 ± 290.2, p = 0.005) while BDNF to creatinine ratio (628.1 ± 590.5 vs 110.4 ± 159.5, p <0.001), this ratio is significantly higher compared to healthy women. No significant differences were found in the ratio of glial cell line-derived neurotrophic factors to creatinine.[6]

In the Alkis et al. 2015 study, the mean BDNF was 838 ± 310.8 compared with the control group with 340.2 ± 199.0, according to this study there was an increase in BDNF levels in OAB patients.[11] In the Antunes study Lopes et al., 2011, found an increase in BDNF in OAB patients with an average value of 980.3 ± 1774.8 compared to the control group of 110.4 ± 159.5.[6]

There is evidence that suggest BDNF plays an important role in the inflammatory process including inflammation in the bladder.[17]Increased neurothropin stimulates afferent fibers so that plasticity changes from afferent fibers can increase acetylcholine and decrease nitric oxide so that detrusor overactivity can occur.[12]

Correlation of urine hs-CRP and BDNF levels in menopausal women who experienced OAB and did not experience OAB at H. Adam Malik Hospital Medan

The hs-CRP increase was significantly higher for chronic inflammation and LUTS symptoms in OAB patients. Patients with an increase in serum hs-CRP ≥ 3 mg / dL had symptom urgency (82.1%) compared with serum hs-CRP levels <0.3 mg / dL (34.9%). Increased serum hs-CRP levels are also associated with low maximal urine flow rates. The median hs-CRP score was also significantly higher in OAB women compared to normal women.[5,8]

From the Bhide study, 2018, there was a significant positive correlation between BDNF and symptom severity using the OAB symptom score with r = 0.649. Chronic inflammation affects the development of OAB.In a study by Wang et al., which compared BDNF in patients with OAB, BDNF improvement in OAB patients compared to non OAB with Odds Ratio (OR) = 11.95 compared with OR = 1.65, p <0.001. This shows a positive correlation between BDNF and symptom severity as measured by the OAB symptom measurement scale.[4,13]

Aging is associated with a slight and chronic increase in some inflammatory mediators of serum produced by neutrophils, activated lymphocytes, NK cell macrophages, and some non-lymphoid cells such as astrocytes, endothelial cells and smooth muscle cells, inflammatory mediators such as TNF-α, IL -6, and IL-1ß. TNF-α and IL-1ß with IL-6 can stimulate each other's production.[39]Proinflammatory cytokines interleukin-6 (IL-6) appear to be the main regulator by promoting the synthesis of de novo from hs-CRP.[9,14] hs-CRP from the *lectin-like oxidized low density lipoprotein receptor-1* (LOX-1) is associated with induction of complement activation, leukocyte infiltration, modification of the vascular response to vasodilation and LDL-ox oxidation in endothelial dysfunction.[14] Endothelial dysfunction causes

vasoconstriction or arterial spasm. As a result, platelet activation and release of substances such as thromboxane occur which have a vasoconstriction effect which increases the risk of ischemic disease.[15] During inflammation, bladder release of inflammatory mediators including neurotrophin causes peripheral afferent ends to be sensitive so that nerve function changes and neuroplasticity in the entire afferent network.[46]BDNF is a neurotropic factor secreted in the urothelium and sensory nerves in the bladder. BDNF also plays an important role in chronic inflammation. This shows that BDNF can be a biomarker for OAB diagnostics.[4,7,16]

IV. CONCLUSION

There is a moderate positive correlation between *hs-CRP* and BDNF in OAB patients. This means that increasement in OAB levels is followed by an increasement in BDNF levels, while in non-OAB patients, it shows an insignificant correlation, this suggests that an increase in *hs-CRP* levels in menopausal women was found to be higher or lower when these women with OAB showed a trend that *hs-CRP* affect the occurrence of *Overactive bladder*.

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REFERENCES

1. Reid, R., Abramson Beth L., Blake Jennifer., Desindes Sophie., Dodin, Sylvie &et al. 2014. Managing Menopause. SOGC Clinical Practice Guideline; 36(9).
2. Rusda Muhammad. 2014. Studi Tentang Menopause Di PuskesmasPintu Padang Dan PuskesmasDanauMarsabutKabupatenTapanuli Selatan;32.
3. Westhuyzen, J., Healy, H. 2000. Review: Biology and Relevance of C-Reactive Protein in Cardiovascular and Renal Disease. Annals of Clinical and Laboratory Science;30(2)
4. Bhide, AA. 2016. To Investigate the Role of Urinary Brain Derived Neurotrophic Factor (BDNF) Measurement in the Assessment of Lower Urinary Tract Symptoms in Women. University of London.
5. Tomaszweski J, Post menopausal overactive bladder, Menopausal review, 6, 313-329
6. Antunes-Lopes Tiago, Carvalho-Barros Sergio, Cruz Celia-Duarte, Cruz Fransisco, Martins-Silva Carlos. 2011. Biomarkers in Overactive Bladder : A New Objective and Noninvasive Tool ?Hindawi.
7. Chung DS,. Liu Ht,. Lin H,.Kuo CH. 2011. Elevation of Serum C Reactive Protein in Patients with OAB and IC/BPS Implies Chronic Inflamation in The Urinary Baldder. Neurology and Urodynamics 30:417-420
8. Kupelian, V., Rosen, RC., Roehrborn, CG., Tyagi, P., Chancellor, MB., McKinlay, JB. 2012. Association of Overactive Bladder and C-Reactive Protein Levels: Results from the Boston Area Community Health (BACH) Survey. BJU Int;110(3):401-407
9. Chuang FC, Liu HT, Wang LY, Kuo HC. Overactive Bladder Changes with Time : a 5 year Longitudinal Follow Up of Changes in Overactive Bladder Distention. Neurology Urodyn. 28(1) : 78-81
10. Chae J, Yoo EH, Jeong Y, Pyeon S, Kim D. 2018. Risk Factors and Factors Affecting the Severity of Overactive Bladder Symptomps in Korean Women Who Use Public Health Centers. Obstet Gynecol Scl;61(3):404-412.
11. Alkis O, Zumrutbas A, Toktas E, Aybek H, Aybek Z. 2015. The Use of Biomarkers in the Diagnosis and Treatment of Overactive Bladder. Can We Predict the Patients who Will be Resistant to Treatment ? Neurology and Uridynamics. 36(2); 390-393.
12. McFerren SC, Gomelsky ALin. 2015. Treatment of Overactive Bladder in the Elderly Female: The Case for Trospium, Oxybutynin, Fesoterodine, and Darifenacin. Drugs Aging;32:809-819
13. Wang LW, Han XM, Chen CH, Ma Y, Hai B. 2014. Urinary Brain-Derived Neurotrophic Factor : a Potential Biomarker for Objective Diagnosis of Overactive Bladder. Int Urol Nephrol. 46(2):341-347.
14. Baziad, Ali. 2003. Menopause dan Andropause. Yayasan Bina Pustaka Sarwono Prawirohardjo. Juni.
15. Miller, C. N., Brown, L. M., Rayalam, S., Della-Fera, M. A., & Baile, C. A. 2012. Estrogens, inflammation and obesity: an overview. Frontiers in Biology, 7(1), 40–47
16. Kuo HC, Liu HT, Shie JH. 2013. Potential Urine and Serum Biomarkers for Patients with Overactive Bladder and Intertitial Cystitis/Bladder Pain Syndrome. Tzu Chi Medical Journal; 25: 13-18.