

# Difference of Serum BDNF Levels Between Schizophrenic Patients with Smoking in Batak Male and Controls

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**ABSTRACT- Background:** Schizophrenia is a severe psychiatric disorder, generally affects approximately 1% of the world population but the pathogenesis of schizophrenia is still unclear. Accumulating evidence shows that brain-derived neurotrophic factor (BDNF) may be involved in the pathophysiology of schizophrenia. Use of nicotine associated with upregulation of BDNF in the serum. Based on the higher smoking rates among schizophrenic patients and the close relationship between nicotine and BDNF, as well as the repeatedly found alternations of BDNF levels in schizophrenia, many studies have suggested that smoking could play a role in the altered BDNF levels of schizophrenic patients.

**Methods:** Serum BDNF levels were measured in 68 Batak males, who smoke (34 subjects with chronic schizophrenia, which was diagnosed with MINI-ICD X and 34 subjects non-schizophrenia as controls), all subjects were aged 20-60 years old, did not suffering from other mental disorders, neurologic disease, and no history of alcohol and other substances except tobacco. Serum BDNF was analyzed with the Quantitative sandwich enzyme immunoassay technique by the use of Quantikine ELISA Human CXCL8/IL-8 HS (R&D Systems, Inc., Minneapolis, USA).

**Results:** The serum BDNF levels were lower in the schizophrenic patients with smoking in Batak males than in the control subjects, reaching statistically ( $26.228 \pm 5.722.5$  pg/ml) vs ( $33.148 \pm 7.290.4$  pg/ml).

**Conclusion:** There was a significant difference in serum BDNF levels between schizophrenic patients with smoking in Batak males and controls.

**Key-words-** Schizophrenia, Batak male, Smoking, Brain-derived Neurotrophic Factor

## INTRODUCTION



Schizophrenia is a psychotic disorder that is generally characterized by distorted thinking and perception of the fundamental and distinctive, and therefore affects the unnatural (Inappropriate) or blunt (blunted) <sup>[1]</sup>. Schizophrenia is a severe and chronic mental disorder with a high prevalence (about 1% of the general population), usually beginning before the age of 25, lasting throughout life, and of people from all social classes <sup>[2]</sup>. The etiology and pathophysiology of schizophrenia have not been explained so far. Various changes in the central nervous system can lead to clinical manifestations of the disease. Neurotrophin plays an important role in regulating the development and maintenance of peripheral and central nervous system functions.

The neurotransmitter deficit is considered an underlying epiphenomenon against the disorganization of neurotrophin <sup>[3]</sup>.

Brain-derived Neurotrophic Factor (BDNF) is a highly involved protein in the development of nervous systems throughout the species, and in the regulation of synaptic transmission. <sup>[4]</sup> Brain-derived Neurotrophic Factor (BDNF), a member of the neurotrophic derivative, is common in the brain of adult mammals, plays an important role in the development, regeneration, survival, maintenance and neuron function <sup>[5,6]</sup>. BDNF levels range from 6.186 to 42.580 pg/ml. <sup>[7]</sup> BDNF is essential for the survival of neurons in the CNS. In addition, in vivo applications show BDNF has protected various neurons from brain injury. The neuroprotective effects of BDNF are observed when received intravenously after the onset of focal cerebral ischemia <sup>[8]</sup>.

The smoking rate among schizophrenic patients is estimated to be between 40% and 90%, higher seen among the general population or individuals with severe mental illness. The reasons for smoking widely are not well understood in schizophrenic patients, but these patients may try to reduce the side effects of antipsychotic drugs to reduce the negative symptoms and/or cognitive deficits associated with schizophrenia, suggesting that

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tobacco or nicotine smoking serves as a form of self-medication. [5] Smoking is the most precise but dangerous way to take nicotine because it can maximize the chance of nicotine dependence. Smoking will deliver large doses of nicotine into the brain's "reward" circuitry and also deliver various carcinogenic substances and various toxins that can destroy cells in the liver, lungs and other tissues [9].

Changes of BDNF have been found to modulate some addictive behaviors are associated with the misuse of certain drugs. A study conducted by Kim et al found that serum BDNF levels were measured in smokers and non-smokers supported the idea of a possible association between BDNF and smoking. They found that group smoking was significantly lower in BDNF levels in the baseline with BDNF serum levels significantly higher in its rise after two months of quitting [10].

Furthermore, plasma levels of BDNF in smokers increased significantly from baseline in the first month and the second month of abstinence circumstances; show that BDNF may play a role in the pathophysiology of the nicotine dependence and Research abstinence. [5] Kenny and his colleagues showed that acute nicotine exposure to lower levels of BDNF while chronic nicotine administration increases BDNF levels in the hippocampus [11].

In the study of Zhang *et al.* [5] found that serum BDNF levels of schizophrenic patients were significantly higher in smokers (7.8±3.2 ng/ml) than non-smokers (6.4±2.1 ng/ml). Furthermore, higher serum levels of BDNF are associated with large numbers of cigarettes smoked.

Based on the above researchers are interested to see the differences in levels of serum BDNF in patients with schizophrenic who smoked and individual Batak male vagabond who smoke and do not suffer from schizophrenia as a control in Mental Health Hospital Installation. Prof. DR. M. Ildrem Medan, which in the end is expected to provide information to the clinician. Researchers are interested in choosing male schizophrenic patients where smoking schizophrenic patients are mostly male and interested in choosing Batak ethnic because the majority of schizophrenic patients who are hospitalized are Batak ethnic.

## MATERIALS AND METHODS

This is a comparative analytical study of numerical unpaired with a cross-sectional study, namely:

**Group I-** Group of schizophrenic male patients Batak, who smoke

**Group II-** Batak Men, who smoke and do not suffer schizophrenia (Control).

This study was performed at the Inpatient Mental Health Hospital under the guidance of Prof. Dr. M. Ildrem Medan in the period of April 2016-July 2016.

**Group I Inclusion Criteria-** Schizophrenic patients, who have been diagnosed by Mini ICD X, Age between 20-60 years old, Male gender, Batak ethnic, Smoking, Chronic schizophrenic patients with stable phase, Willing

to respond and interview able. Exclusion Criteria; Suffering from other mental disorders having a neurologic disease, History of alcohol use and other substances except for tobacco.

**Group II Inclusion Criteria-** Batak ethnic, Age between 20-60 years old, Gender Male, Smoking, willing to be respondent and can be interviewed. Exclusion Criteria; Suffering from Mental Disorders, Having a family history with a mental disorder, Having a neurologic disease, History of alcohol use and other substances.

The sample was obtained by non-probability sampling type consecutive sampling [12]. The minimum sample size needed to detect the difference of BDNF serum level can be concluded that the sample size for each group is 34 subjects, so all the sample in this research is 68 subjects.

Preparatory stages included the management of research permits from research sites and ethics committees of the Faculty of Medicine, University of North Sumatra. BDNF serum levels were analyzed with the Quantitative sandwich enzyme immunoassay technique by the use of Quantikine ELISA Human CXCL8/IL-8 HS (R&D Systems, Inc., Minneapolis, USA) [7]. After the data serum BDNF results have been there will be done data processing. Data processing is done with the help of SPSS software. Data normality test was performed on each group using Saphiro-Wilk test. The hypothesis test used is t-independent if it meets the requirements of the test, and the alternative if it does not meet [13].

## RESULTS

The study obtained 34 subjects for the schizophrenic group and 34 subjects for the control group. Subjects for the schizophrenic group were individuals of batak ethnic who smoked with schizophrenia established by structured interviews using MINI ICD-X in inpatient at Prof. Dr. M. Ildrem hospital North Sumatra. Subjects in the control group were obtained from male individuals who smoked and did not suffer from schizophrenia. For the control group the research subjects were obtained from individuals who were willing to be samples and meet the inclusion criteria of the study.

Body Mass Index (BMI) subjects in the schizophrenia and control group were normoweight, 27 (79.4%) and 24 (70.6%), respectively. Chi square test was conducted to find out whether there was a difference of BMI sub-variable proportion between schizophrenic and control group. The final result of this test was obtained after the subgroup of sub-variable of underweight-normoweight. This is done because in the test with the sub-variables are not combined, obtained 2 cells with a value of less than 5, so the results of his chi square test is not feasible to read. After the merger of cells, no cells with a hope value of less than 5. From fischer test obtained p-value = 0.144, so it can be concluded that there is no significant difference in the proportion of BMI sub-variables between schizophrenic and control groups.

**Table 1:** Baseline Characteristics Demographic of study sample Schizophrenic patient and controls

Variabel	Schizophrenic		Control		$\Delta/x^2$	P
	x / f	SD / P	x / f	SD / P		
Age (year)	38.88	6.85	35	10.43	3.88	0.075*
<b>Education</b>						
Junior high school	4	11.8%	1	2.9%		
High school	28	82.4%	26	76.5%	3.202	0.150**
Diploma	2	5.9%	3	8.8%		
Bachelor	0	0%	4	11.8%		
<b>Marital status</b>						
Not married	21	61.8%	13	38.2%	3.765	0.052
Married	13	38.2%	21	61.8%		
<b>Body Mass Index</b>						
underweight	2	5.9%	0	0%	2.138	0.144***
Normoweight	27	79.4%	24	70.6%		
Overweight	5	14.7%	10	29.4%		

x: mean; f: frequency; SD: standard deviation; P: proportion;  $\Delta$ : average difference;  $x^2$ : chi square; \*) t- independent test, after data normality test (shapiro-wilk test, p = 0,070); \*\*) fischer test, the p value obtained after the merger of cells as in the attachment; \*\*\*) \*\*) chi square test

**Table 2:** Differences BDNF serum levels between the Schizophrenic and Control Group

Variable	Schizophrenic		Control		$\Delta$	P
	X	SD	X	SD		
Level serum BDNF	26.228	5.7225	33.148	7.2904	6.9201	0,001*

x: Mean; SD: Standart deviation;  $\Delta$ : average difference; \*) t-independent test, after data normality test (shapiro-wilk test, p = 0.342)

Table 2 shows differences in BDNF serum levels between schizophrenic and control groups. The mean serum BDNF concentration of the subjects in the schizophrenia group was 26.228 pg / ml with standard deviation 5.722,5 pg/ml, while in the control group the serum BDNF concentration of the study subjects was 33.148 pg / ml and standard deviation of 7.290.4 pg / ml. Normality data test of this age variable was done with shapiro-wilk test, and got result value p=0.342, and because p value obtained greater than 0.05, can be concluded that data is normal distribution. Furthermore, t-independent test was performed to determine whether there was a difference in serum BDNF level between the schizophrenic group and the control, and p = 0.001 with mean difference was 6.920,1 pg/ml, so it was concluded that there was significant difference in serum BDNF level between schizophrenic group and control.

**DISCUSSION**

This is a comparative analytical study of numerical unpaired with a cross-sectional study. Samples obtained by non-probability sampling type consecutive sampling.

From the results of the study were showed that in the baseline there was no significant difference in demographic characteristics.

The effect of age in serum levels of BDNF according to a previous study by Wilkosc *et al.* [14] in the healthy people, BDNF levels increased with age to reach adulthood in the third decade of life, and began to decline in late adulthood. In this study the average age of research subjects in the schizophrenic group was 38.88 years with standard deviation 6.85 years, while in the control group, the age of the study subjects was 35 years and standard deviation 10.43 years, so it was concluded that there was no significant difference in age research subjects between schizophrenic groups and controls. This suggests that in this study there was no age effect on serum levels of BDNF.

The results showed that body mass index (BMI) of the subjects in the schizophrenic and control group was normoweight, as many as 27 subjects (79.4%) and 24 subjects (70.6%), respectively. From fischer test obtained p value= 0.144, so it can be concluded that there is no significant difference in the proportion of BMI sub-variables between schizophrenic and control group.

This suggests that there was no BMI effect on serum BDNF levels. Previous studies have shown that plasma BDNF levels in healthy people decrease significantly with weight gain. Araya *et al.* [14] also confirmed the relationship between body weight and plasma levels of BDNF in overweight and obese people who had gone on a diet. BDNF levels increased after 3 months on a diet.

The results shown, there was a significant difference in serum BDNF level between Batak male schizophrenic group who smoked and controlled. This study is the first study to measure levels of serum BDNF in Batak ethnic of male who suffered from schizophrenia and Batak male, who do not suffer schizophrenia.

Previous studies by Cui *et al.* [15] were shown the serum BDNF levels were significantly lower in the schizophrenic group when compared with the control group. This was also in accordance with Koeva *et al.* [3] research in 2014 indicating that BDNF levels were significantly reduced in serum schizophrenic patients compared with controls ( $10.14 \pm 3.08$  vs.  $12.32 \pm 2.41$ ,  $p = 0.009$ ).

In a systematic review on 188 studies from 46 countries, the median prevalence of schizophrenia ranged from 4 to 7 per 1000 persons, depending on the type of prevalence. Despite low prevalence of schizophrenia, it is one of the great contributors to global burden of disease [16]. The theory that changes in the metabolism of neurotropic factors are the pathophysiological event of schizophrenia may be related to the mal-development phenomenon that has been postulated for groups of psychotic disorders and supported by studies that explain changes in the level of neurotrophic factors and their receptors in schizophrenia [3].

BDNF modulates the synthesis of neurotransmitters, metabolism and neuronal activity. It is involved in the development of dopaminergic systems, and the mesolimbic dopamine system. Abnormal BDNF signals may affect neuronal differentiation and synaptic function, leading to changes in brain development and function. Neuro-developmental abnormalities and dys regulated dopamine systems had been implicated in the pathophysiology of schizophrenia. Therefore, BDNF may be a marker of abnormal neuronal development and neurotransmission in schizophrenia. Decreased serum levels of BDNF have been reported in neuroleptic-free patients with schizophrenia compared with healthy controls, and in chronic schizophrenic patients taking antipsychotics [4].

This study was very consistent with previously reported studies showing that there is a difference in serum BDNF levels in schizophrenic and control patients, the chances of this difference in serum BDNF levels being due to the pathophysiology of schizophrenia itself.

This study had limitations where this study does not explain the state of smoking behavior on the subject of research so it is necessary to do further research that discusses smoking behavior in schizophrenic patients. In the study, Zhang *et al.* [5] investigated the association of serum BDNF levels by smoking in schizophrenic patients. In this study, they found that smokers with

schizophrenia BDNF levels increased significantly and had fewer positive symptoms than nonsmokers in schizophrenia. In addition, smoking with more numbers of cigarettes correlated with higher BDNF levels and fewer negative symptoms.

## CONCLUSIONS

In this study, we were concluded that there was a significant difference in the serum BDNF level between the schizophrenic groups of the Batak male, who smoked with control. The mean levels of serum BDNF subject of research in the schizophrenic group of the Batak male, who smoke were 26.228 pg/ml with a standard deviation of 5.722.5 pg/ml whereas, in the control group, the levels of serum BDNF research subjects were 33.148 pg/ml and a standard deviation of 7.290.4 pg/ml.

As far as research has been done there has been no specific research on ethnic differences against BDNF levels. Does ethnicity affect BDNF serum levels? Further studies are needed to see how serum BDNF levels of schizophrenic patients are to other ethnicities. It is necessary to conduct further research to investigate the effect of smoking behavior on schizophrenic patients on BDNF serum levels.

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