

## Original Research

# Effect of Aerobic Exercise on *Brain-derived Neurotrophic Factor* (BDNF) Serum Level in Stroke Subjects with Cognitive Function Impairment

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### ABSTRACT

**Background:** Cognitive impairment is the most frequent complication of stroke. However, aerobic exercise is considered to have potential effect in inhibiting the post-stroke cognitive degradation and increasing cognitive performance through neuroplasticity-influenced long term potentiation in hippocampus.

**Aim:** To determine the effect of aerobic exercise on *brain-derived neurotrophic factor* (BDNF) serum level in stroke subjects with cognitive function impairment.

**Material and Methods:** Experimental pre-post study on sub-acute stroke male and female, 12 subjects on each group. Intervention group given standard therapy and aerobic exercise using static cycle. Control group treated with standard therapy 30 minutes/session 3x/week, for 6 weeks. Parameter being evaluated was BDNF serum level.

**Result:** No significant difference ( $p=0.21$ ) in BDNF serum level in both control group ( $246.03\pm 40.81$  pg/ml) and intervention group ( $280.98\pm 73.53$  pg/ml) after treated with treatment. Although there was a significant increase of BDNF serum level in the intervention group ( $p<0.001$ ) with pre-intervention mean value of  $1.96\pm 60.69$  pg/ml and post-intervention mean value of  $280.98\pm 73.53$  pg/ml. Similar to the intervention group, there was a significant increase in BDNF serum level ( $p<0,001$ ) in control group, with pre-intervention mean value of  $136.39\pm 76.32$  pg/ml and post-intervention mean value of  $246.03\pm 40.81$  pg/ml.

**Conclusion:** No significant difference in BDNF serum levels in intervention group after aerobic exercise program with a static cycle and standard therapy 3x/week for 6 weeks, when compared to the control group that only received standard therapy, although both control and intervention groups showed significant difference before and after the intervention.

**Keywords:** *aerobic exercise, cognitive function impairment, serum brain-derived neurotrophic factor, BDNF, static cycle, stroke*

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## **Introduction**

Stroke is the main cause of disability and death in Indonesia, with its prevalence increasing every year from 6 % in 2007 to 7 % in 2013.<sup>1</sup> The most common complication of stroke is cognitive impairment. The risk of developing cognitive impairment after stroke is increased to three times compare to non-stroke person. Around 50-75% stroke patients suffer from cognitive impairment with the prevalence of dementia 3 months after stroke counts for approximately 23,5-61%. This cognitive impairment increase the risk of mortality three times than the stroke patient with no cognitive impairment. Cognitive impairment may contribute into participational decrease on daily activities, decrease of quality of life, increase of mortality and economic burden in society.<sup>2</sup> This condition might be due to medical and surgical advance in stroke managements alleviating the life expectancy of stroke patients, thus the increasing role of stroke rehabilitation management.

Aerobic exercise is one considerably easy, cheap and readily available non-pharmacological intervention to increase cognitive performance and inhibit cognitive function decline after stroke. Previous study already explained how the mechanism of neuroplasticity affects long term potentiation in hippocampus. This study examines the effect of aerobic exercise on BDNF serum level in stroke subjects with cognitive impairment.

We found no previous study about the effect of aerobic exercise on BDNF serum level in stroke subjects in Indonesia. This research was done in the intention to further explore the effect of aerobic exercise on serum BDNF level as a marker of brain plasticity on stroke subjects. We hypothesized aerobic exercise will

increase the serum BDNF level in stroke subjects with cognitive impairment. We hope the result of this study can be considered for stroke rehabilitation management.

Brain-derived Neurotrophic Factor (BDNF), a base protein, is one of the family of growth factors and neurotrophins. BDNF is expressed into nervous system dan non neuronal tissues.<sup>3</sup> BDNF serum level is measured quantitatively using Enzyme Linked Immune-Sorbent Assay (ELISA) method.

## **Material and Methods**

This study was an experimental pre-post study on male and female subacute stroke subjects with cognitive impairment, 12 subjects on each control group and intervention group. The intervention group was enrolled into standard therapy and aerobic exercise program using static cycle, meanwhile the control group was enrolled into a standard therapy program for 6 weeks, 3x/week, 30 minutes each session. Cognitive function was assesed using Mini Mental State Examination (MMSE). Inclusion criteria for this study were stroke subjects with mild to moderate cognitive function impairment (MMSE 15-26), stable hemodynamic, independent ambulation with or without assistive device, and able to comprehend and follow verbal instruction. Subjects who regularly exercised, subjects with dementia and or depression, subjects with lower extremity neuromusculoskeletal disorder, and subjects with balance disturbance were excluded. Parameter evaluated was serum BDNF level by ELISA method using Elabscience Human BDNF (Brain Derived Neurotrophic Factor) ELISA Kit reagent.

Post-stroke recovery occur alongside BDNF serum level increase. Data analysis was

done using SPSS to confirm the effect of aerobic exercise on BDNF serum as a marker of brain plasticity in stroke subjects with cognitive function impairment.

**Result**

Total participants of this study were 24 subjects. Mean age of the participants was 57 years old on the control group, 53 years old on intervention group. Mean body mass index was 23.95 kg/m<sup>2</sup> on control group and 25.29 kg/m<sup>2</sup> on intervention group showing overweight anthropometric profile. The mean length of formal education on both groups showed 12 years on control group and 10 years on intervention group, showing mostly came from senior high school. Both group had equal side of lateralization proportion. No significant

difference (p= 0.21) in pre-intervention serum BDNF level on control group (246.03±40.81 pg/ml) and on intervention group (280.98±73.53 pg/ml).

There were significant increase of BDNF serum level in the intervention group (p<0.001) with a mean level before intervention of 81.96±60.69 pg/ml and mean level after intervention of 280.98±73.53 pg/ml. Similar to the intervention group, there was a significant increase in serum BDNF levels (p<0.001) in control group, with a mean level before intervention of 136.39±76.32 pg/ml and mean level after intervention of 246.03±40.81 pg/ml.

Table 1. Baseline characteristics and homogeneity test

Characteristics	Control Group (n=12)		Intervention Group (n=12)		P value
	N (%)	Mean±SD	N (%)	Mean±SD	
Sex					0.62 <sup>b</sup>
Male	10 (83.33)	-	10 (83.33)	-	
Female	2 (16.67)	-	2 (16.67)	-	
Age (years old)	-	57.42 ± 8.96	-	53.17 ± 7.35	0.76 <sup>a</sup>
Body Mass Index (kg/m <sup>2</sup> )	-	23.95 ± 5.63	-	25.29 ± 4.04	0.97 <sup>a</sup>
Years of Formal Education	-	12.25 ± 4.14	-	10.5 ± 2.39	0.09 <sup>a</sup>
Lateralization					1.00 <sup>b</sup>
Right	6 (50%)	-	6 (50%)	-	
Left	6 (50%)	-	6 (50%)	-	
Hypertension					0.36 <sup>b</sup>
Yes	10 (83.33%)	-	8 (66.67%)	-	
No	2 (16.67%)	-	4 (33.33%)	-	
Diabetes mellitus					0.19 <sup>b</sup>
Yes	2 (16.67%)	-	5 (41.67%)	-	
No	10 (83.33%)	-	7 (58.33%)	-	
Dyslipidemia					0.68 <sup>b</sup>
Yes	8 (66.67%)	-	7 (58.33%)	-	
No	4 (33.33%)	-	5 (41.67%)	-	
Smoking					0.69 <sup>b</sup>
Yes	6 (50%)	-	5 (41.67%)	-	
No	6 (50%)	-	7 (58.33%)	-	
BDNF serum level pre-intervention (pg/ml)	-	136.39 ± 76.32	-	81.96 ± 60.69	0.76 <sup>a</sup>

Table 2. Comparison of serum BDNF level after intervention between control and intervention group

Parameter	Control group	Intervention group	p value	Effect size
Serum BDNF level post-intervention (pg/ml)	246.03 ± 40.81	280.98 ± 73.53	0.21	0.23

## Discussion

Subjects of this study were male and female proven to be eligible to be enrolled in the study by physical and supporting examination. Mean participant age was 57 years old on control group and 53 on intervention group (Table 1), both group were still in the productive age, necessitating management in post stroke cognitive impairment to achieve functional independence. Mean body mass index in control group was 23.95 kg/m<sup>2</sup> and in intervention group was 25.29 kg/m<sup>2</sup>. These showed an averagely overweight antropometric profile of the participants. Mean length of formal education on control group was 12 years, on intervention group was 10 years with mostly came from senior high school.

Subject characteristics data analysis showed no difference on sex, body mass index, and length of formal education between both groups. No significant difference was found on risk factors such as hypertension, diabetes, dyslipidemia, and smoking, neither on pre-intervention serum BDNF level on both groups.

Strongest hypothesis explaining the mechanism of BDNF increase after physical exercise is through the modulation of neurotrophin signaling pathway. Many studies have reported about the correlation between

Table 3. Comparison of serum BDNF level after intervention between control and intervention group

Group	Before intervention (pg/ml)	After intervention (pg/ml)	p value
Control	136.39 ± 76.32	246.03 ± 40.81	<0.001
Intervention	81.96 ± 60.69	280.98 ± 73.53	<0.001

between the increasing level of physical activity with cognitive function restoration, and hippocampus volume on geriatrics.<sup>4</sup> Physical activity can induce FNCD5 production through coactivation of PGC-5 and ERR $\alpha$ , then FNCD5 with the help of protease transform into irisin, a polypeptide hormone which may increase energy expenditure. Irisin could pass blood brain barrier and induce BDNF gene expression on hippocampus. Physical exercise also induce expression and release of IGF-1 by the liver, which in turn stimulate BDNF gene expression.<sup>5</sup>

Study from Begliumini et al. reported that plasma BDNF level on adult male is highest in the morning, lowest at night. Low BDNF level correlates with the circadian secretion cycle. BDNF level is similar with cortisol level in human, with short half-life in plasma ( $t_{1/2}$  = 0.92 minutes).<sup>6</sup> Cortisol is the most important glucocorticoid in human, affecting bone metabolism, blood pressure, and plays an important role in central nervous system homeostasis.<sup>6</sup>

Highest BDNF expression occurs on the central nervous system, controlling synaptic plasticity and connectivity in adults mainly through tropomyosin receptor kinase B (TrkB) pathway. BDNF circadian cycle and or TrkB receptor acts on several sites in the brain (hippocampus, frontal cortex, visual cortex,

superior colliculus, and cerebellum), thus we may found elevation of BDNF expression on hippocampus, central area for memory and learning.<sup>7-9</sup>

This study showed no significant difference of serum BDNF level between both groups, it may happen due to short physical exercise duration. Carvalho *et al.* and Hasan *et al.* stated that the positive effects of aerobic exercise on cognitive function restoration, inhibition of cognitive decline, and BDNF serum level may be observed the earliest after 8 weeks of the exercise, lasting until 6 months after.<sup>10,11</sup>

Our previous study found that there was a significant increase of MMSE after aerobic exercise using static cycle 3x/week for 6 weeks on stroke patients with cognitive function impairment.<sup>12</sup> There was a significant difference of global cognitive function on control group ( $p < 0.001$ ) and intervention group ( $p < 0.001$ ). This showed that standard therapy only or a combination of static cycling aerobic exercise with standard therapy may improve global cognitive function of post stroke subjects. This goes in hand with what Valera *et al.* found, stating that moderate intensity static cycle aerobic exercise (40-60% heart rate reserve) 3x/week, 30 minute/session for 6 months increases global cognitive function measured using MMSE.<sup>13</sup>

Table 2 showed there were significant changes ( $p < 0.001$ ) in the mean serum BDNF level before and after intervention in the control group ( $p < 0.001$ ) and intervention group ( $p < 0.001$ ). Although, comparison in serum BDNF level after intervention did not reveal a significant difference ( $p = 0.21$ ) (table 3).

Exercise intensity plays an important role in regulating the BDNF on population with

neurological disorder by way of cumulative effect from regular exercise. Baseline BDNF level vary between studies within similar population, and studies comparing healthy population and population with neurological disorder. Basal BDNF level difference may be influenced by age, sex, diurnal cycle fluctuation, nutritional status, metabolic and immunologic disorder.<sup>14</sup>

Several confounding factors of BDNF level need to be considered such as physical activity, sleep pattern, nutritional intake, light, and more. Evaluation of the effects of Circadian cycle on plasma BDNF level is done by controlling the confounding factors such as postural change, behavioural status, environmental condition and use of *Constant Routine* (CR) protocol during night and day. CR protocol is a condition of being awake in semirecumbent position with constant lighting for at least a minimal one circadian cycle (>24 hours), with available food and drinks along the day and night. CR protocol eliminates behavioural changes periodically and maintain constant environment condition, allowing accurate evaluation of endogenous circadian cycle variation on physiological condition.<sup>15</sup> Repeated sampling on various times of the day also may represent the correlation between the disease and the recovery process.<sup>16</sup>

Single nucleotide polymorphism on BDNF gene also affect BDNF secretion level and rhythm. In human, single nucleotide polymorphism on BDNF gene causing substitution of valine into methionine on 66 codone (Val66Met) correlates to low activity-dependent release BDNF.<sup>17</sup> Patient with BDNF polymorphic gene has lower BDNF level in the circulation.

Low BDNF serum level is correlated with increased risk of recurrent stroke, poor functional outcome, and high mortality rate. BDNF signal depends on the genetic variation which could affect the individual response during stroke recovery.<sup>18</sup>

Kotlega *et al.* stated that having the lowest tertile of BDNF level increase the risk of low functional outcome on 2 years and 7 years follow-up. Similar result was found on a study stating low baseline BDNF level correlates to higher 3 months mortality and lower functional outcome measured by *modified Rankin Scale* (mRS). Framingham study of 10 years follow-up found that a low BDNF level correlates with increased risk of stroke and *transient ischemic attack* (TIA). BDNF plays a major part in the stroke incidence and post-stroke functional outcome.<sup>18</sup>

Considering the importance of BDNF in obtaining information of disease progression and its recovery, it is urgent to acquire data about BDNF level changes along the day, because circadian variability of plasma BDNF can cause misinterpretation of basal individual BDNF level due to variation of the time chosen to acquire the sample and due to variation of the duration of the sample kept. This study acquired the blood sample during the peak hour of the BDNF secretion which is in the range of 08.00-12.00 AM with samples being kept around 2 weeks to 2 months.

Aerobic exercise is an exercise intervention giving positive effects on neurologically disturbed patients, such as stroke, found to increase functional capacity and motor performance through increase of cardiorespiratory fitness, increase of cerebral blood flow, changes in neurotransmitter release, central nervous system structural changes

related to sinaps plasticity by way of increasing BDNF expression.

## Conclusion

No significant difference of BDNF level after 6 weeks, 3x/week of aerobic exercise and standard therapy compared to standard therapy only. But there were significant increases of BDNF level on each group before and after the intervention.

Although no significant difference was found, aerobic exercise still can be recommended to increase motor control, to restore cardiopulmonary endurance, and to improve cognitive function on post stroke patient, so as to encourage the patient to participate in daily living activities actively and maximize the quality of life.

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