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Original Article

The Correlation Between Folic Acid Supplementation and Change in Cognitive Function in Elderly
(A Study of The Effect of Folic Acid Supplementation on Homocysteine Levels)

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Abstract

Background : A good cognitive function is one of the things that affect the quality of life of the elderly. Decreased cognitive function in elderly can be caused by physiological or pathological processes. Increased homocysteine is one of risk factors associated with decreased cognitive function. Folic acid supplementation has been shown to reduce homocysteine levels. This study was aimed to know the relationship between folic acid supplementation and change in cognitive function in elderly.
Methods : This research is a quasi-experimental study at Pucang Gading Nursing Home, Semarang. A total of 30 subjects were divided into 2 groups, namely 15 treatment subjects (given folic acid supplementation 1 mg/24 hours) and 15 control group subjects (given placebo), 1 subject dropped out due to death. The study was conducted for 12 weeks, assessment of homocysteine level and cognitive function (with MoCA Ina) was carried out before and after the study.
Results : There was no relationship between folic acid supplementation and changes in homocysteine level (*p* 0.322). There is a relationship between folic acid supplementation with change in cognitive function in elderly (*p* 0.000). There is a relationship between changes in homocysteine level and global change in cognitive function in elederly (*p* 0.018).
Conclusion : There is a significant relationship between folic acid supplementation and change in cognitive function in elderly.

Keywords : Elderly, cognitive function, MoCa Ina, homocysteine, folic acid

INTRODUCTION

Elderly is a group of people aged over 60 years. The better standar of living and health in Indonesia then the number of elderly in Indonesia continue increasing from 7.6% in 2010 to 8.03 % in 2014. Survey Data from the National Socio – Economic Survey (Susenas) on March 2022 shows 10.48% of the population is elderly. The number of elderly keep growing along with the improvement of life expectancy. The number of elderly in Indonesia in 2017 was 23.66 million and predicted to increase more than double on 2035. Globally, by 2030, it is estimated at least 1 in 6 people in the world will age 60 years of older. Currently, the proportion of resident aged over 60 years will increase from 1 billion in 2020 to 1.4 billion. Population resident aged over 60 years in the world will double (2.1 billion) by 2050.

The good cognitive Function is a factor influencing quality life in elderly. As age increases, body experience aging process including brain. The declined brain cell function will cause short term memory loss, reduced ability in decision making and actions, concentration disorder, slowing information processing so that hinder communication process as well as psychic and social life, and physical activities in elderly. [2]

Homocysteine, amino acids containing sulfur, is an intermediate compound formed from methionine metabolism. The high homocysteine level is related to increased risk of heart attack, stroke, Alzheimer's and declined cognitive function. Some studies report improved homocysteine plasma level related to declined cognitive function and cerebral atrophy, as well as to predict the existence of dementia development among middle age and old people with previously normal cognition. [3–5]

The effect of hyperhomocysteinemia on cognitive function may be indirectly caused by previous vascular damage. Imaging examinations show that individuals with hyperhomocysteinemia have silent infarcts, white matter lesions, and brain atrophy associated with decreased cognitive function. Research on nerve cell cultures shows that high homocysteine levels can cause neurotoxicity without previous vascular damage. High homocysteine levels can reduce the availability of methionine with the consequence of affecting the synthesis and degradation of neurotransmitters, both of which are thought to play a role in decreased cognitive function. Folic acid administration has been shown to be able to reduce homocysteine levels, although not consistently in several studies, and in separate studies it has been shown that folic acid administration can improve patient cognitive outcomes. Research conducted by Balk *et al* in America, proved that consumption of folic acid supplements provided better cognitive outcomes. Evaluations were carried out in 5 weeks and 11 weeks after treatment, with significant results in the 11th week in the 1 mg/day folic acid group (control group 0.4 mg/day). Inge Permadhi *et al* found that routine folic acid supplementation of 1 mg/day in the elderly for 6 weeks was able to reduce homocysteine levels by 36.68%. With these data, the study will be conducted for 12 weeks. [6–9]

Montreal Cognitive Assessment Indonesia version (MoCA Ina) is an initial screening of cognitive function, which can be completed in 10 minutes, with 30 points designed to help health professionals detect mild cognitive impairment. The recommended cut-off score for MoCa is 26. MoCA Ina is more appropriate for assessing cognitive function, because it is more sensitive than MMSE in detecting mild cognitive impairment. MoCa Ina can also be completed in less than 10 minutes, thus reducing the influence of fatigue in determining test results. In addition, MoCa more broadly assesses attention, visual-spatial abilities, learning, and executive functions compared to MMSE. [10–13]

Pucang Gading Social Home is a social home managed by the Social Service of the Central Java Provincial Government with elderly people from several regions in Central Java, not only from Semarang area. Thus, it is expected that the elderly in Pucang Gading Social Home have more diverse characteristics and are considered to be able to represent the elderly in Central Java.

METHODS

This study was a quasi-experimental at Pucang Gading Social Home, Semarang. The minimum sample calculation for the experimental design obtained 13 subjects per group, with an estimated dropout of 10%, so that 15 subjects per group were determined. Consecutive sampling was carried out with a total of 30 subjects divided into 2 groups, namely 15 treatment subjects (given 1 mg/24 hours folic acid supplementation) and 15 control group subjects (given placebo), 1 subject dropped out of the control group due to death. Inclusion criteria include being able to read and write and agreeing to participate in the study. Exclusion criteria included elderly people with aphasia, depression, diarrhea, and alcoholism.

The study was conducted for 12 weeks, assessing serum homocysteine levels using the ELISA method and cognitive function (with MoCA Ina) before and after the study. Changes in cognitive function in the elderly based on MoCA Ina were associated with the provision of folic acid supplementation, based on the calculation of the unpaired categorical test statistical method in two groups, and the pre-post-test. Researchers also conducted an analysis to prove the effect of age, gender, education level, body mass index, hypertension, dyslipidemia, diabetes mellitus, on changes in cognitive function in elderly.

TABLE 1
Characteristics of Experimental Subject

Variables	N	%	Control N = 14	Treatment N = 15
Gender				
Man	10	34.48%	6 (43%)	6 (43%)
Woman	19	65.52%	8 (57%)	8 (57%)
Age				
≤ 65 year	7	24.14%	4 (29%)	4 (29%)
> 65 year	22	75.86%	10 (71%)	10 (71%)
Hypertension				
No	19	65.52%	11 (79%)	11 (79%)
Yes	10	34.48%	3 (21%)	3 (21%)
Diabetes Mellitus				
No	22	75.86%	9 (64%)	9 (64%)
Yes	7	24.14%	5 (36%)	5 (36%)
Level Education				
≤ 12 year	19	65.52%	7 (50%)	7 (50%)
> 12 year	10	34.48%	7 (50%)	7 (50%)
Index Mass Body				
Underweight	3	10.34%	1 (7%)	1 (7%)
Normal	23	79.31%	12 (86%)	12 (86%)
Overweight	1	3.45%	1 (7%)	1 (7%)
Obese	2	6.90%	0 (0%)	0 (0%)
Dyslipidemia				
No	19	65.52%	9 (64%)	9 (64%)
Yes	10	34.48%	5 (36%)	5 (36%)

RESULTS

There were 29 subjects who met the inclusion and exclusion criteria during the research period November 2022 – February 2023 with the characteristics listed in Table1.

DISCUSSION

Table 1 describes the demographic and clinical characteristics of the study subjects. All numeric variables have been tested for data normality, and show a normal distribution. All subjects in the treatment group have been recorded, none of whom experienced nausea, vomiting, diarrhea during 12 weeks of folic acid supplementation. In the initial and final homocysteine examinations, pre-study data were obtained with a mean of 6.4 µmol/L (minimum value 0.33 µmol/L – maximum value 28.83 µmol/L) and post-study data with a mean of 7.77 µmol/L (minimum value 0.02 µmol/L – maximum value 18.16 µmol/L). From these data, only 2 subjects in the pre and post-study results experienced hyperhomocysteinemia, so further analysis used numeric and nominal variables (increased or not increased). Table 2 shows the initial, final homocysteine levels, and their differences, between the control and treatment groups. In the initial homocysteine examination, there was a difference between the control and treatment groups based on the unpaired T-test (p 0.020) where the treatment group had lower serum homocysteine levels

TABLE 2
Serum Homocysteine Level

Information	Control N = 14 (μmol /L)	Treatment N = 15 (μmol /L)	*p*
Initial serum homocysteine	8.88 ± 7.11	4.07 ± 2.33	**0.020***
Final serum homocysteine	8.53 ± 5.55	7.07 ± 3.22	0.391*
Changes in serum homocysteine	0.81 ± 5.19	2.33 ± 2.56	0.322*
	$p = 0.842^{Y}$	$\mathbf{p = 0.013^{Y}}$	

Information: * Independent T-test, ^{Y} Paired T-test; significant when $p<0.05$

TABLE 3
Initial, final, and changes in MoCA Ina of changes in cognitive function

Information	Control N = 14	Treatment N = 15	*p*
Initial MoCA Ina	19.64 ± 5.03	14.06 ± 4.00	**0.005***
Final MoCA Ina	17.00 ± 3.96	18.40 ± 4.96	0.418*
Changes in MoCA Ina	-2.64 ± 3.69	4.33 ± 3.53	**0.000***
	$\mathbf{p = 0.016^{¥}}$	$\mathbf{p = 0.013^{¥}}$	
	z = -2.408	z = +2.405	

Information : * Independent T-test ; $^{¥}$ Paired T-test ; significant when $p < 0.05$

TABLE 4
Connection Change Level Homocysteine Serum and Factor Risk with MoCa Ina

Variables	N	Initial MoCA Ina (Mean ± SD)	Final MoCA Ina (Mean ± SD)	Changes in MoCA Ina (Mean ± SD)	MoCA Ina		Mark *p*
					Getting better	No getting better	
homocysteine Level							
Increase	24	17.4 ± 5.45	18.0 ± 4.75	0.54 ± 5.27	10	14	$p = 0.018$*
No increase	5	13.4 ± 2.60	16.4 ± 2.88	3.00 ± 1.22	5	0	$R = 0.763^{¥}$

Information : *C*hi-square* significant when $p < 0.05$, $^{¥}$ Correlation This

than the control group. In the final homocysteine examination, there was no difference between the two groups, but there was a significant increase in homocysteine levels in the treatment group based on the paired T-test (*p* 0.013), which is contrary to the theory that folic acid administration can reduce homocysteine levels.

This is inconsistent with previous studies that stated that folic acid supplementation can reduce homocysteine levels. Folate acts as a precursor for 5-methyltetrahydrofolate, a methyl donor for the remethylation of homocysteine to methionine so that homocysteine auto-oxidation that produces oxidized disulfide, two protons (H+) and two electrons (e-) that stimulate the formation of ROS is not formed. Folate deficiency indirectly causes an increase in plasma homocysteine concentrations. Folate deficiency also causes low concentrations of S-adenosyl methionine, an important methyl donor needed for epigenetic processes (gene methylation) and for the basis of processing cell metabolism (DNA and protein synthesis). Folic acid supplementation is effective for normalizing increased homocysteine levels so that it can be used to prevent cardiovascular disease. [8,14]

David S. Wald *et al*. proved that giving folic acid supplementation up to 5 mg/ day for 3 months can reduce homocysteine levels by up to 25% (or 3–12 μmol/L) in

patients known to have ischemic heart disease. In a study conducted by Wald *et al*., all subjects had high homocysteine levels, with an average of 20 µmol/L.[15] Kam S. Woo noted a decrease in homocysteine levels from 9 ± 1.7 µmol/L to 7.9 ± 2.0 µmol/L with the administration of 10 mg/day folic acid supplementation for 1 year. The increase in homocysteine levels in the treatment group in this study is still unexplained, but may be related to homocysteine metabolism itself which may involve a genetic role (polymorphism of MTHFR), side effects of other treatments (methotrexate, theophylline, phenytoin, and cyclosporine), chronic diseases (end-stage renal disease, liver dysfunction, and hypothyroidism), which should be examined in this study.[16] Increased homocysteine levels may also be related to red meat consumption and a diet high in methionine, which can be converted to homocysteine. Food groups that are high in methionine include beans, beef, lamb, pork, cheese, shellfish, soy products, eggs, milk, and nuts. Methionine levels that exceed normal levels (13 mg/kgBW) can cause increased homocysteine, and increase the risk of neurodegenerative diseases, especially Alzheimer's dementia.[6,17] In this study, no methionine levels were assessed. All elderly people received the same food from the social care facility manager, in the form of side dishes that had been arranged on plates (not taken by themselves), so it was assumed that the food intake between the two groups was no different.

Table 3 shows that there was a significant difference in the initial MoCA Ina value in the treatment group of 14.06 ± 4.00 compared to the control group of 19.64 ± 5.03, but there was no significant difference in the final MoCA Ina value. In the initial and final results, all study subjects were classified as cognitively impaired (because MoCA Ina <26), so the researchers divided the outcome of cognitive function into improved and not improved (there was no significant difference in changes in MoCA Ina in the two groups, namely an increase in MoCA Ina in the treatment group (p 0.013) and a decrease in MoCA Ina in the control group (p 0.016).

In a review compiled by I Putu Eka Widyadharma, several studies have shown that folic acid supplementation can improve cognitive function outcomes. Chen (2016) provided 1.25 mg/day folic acid supplementation for 60 days in 61 Alzheimer's patients, with improved cognitive function results (based on MMSE) $p < 0.005$.18 Ma (2016) provided 400 µg/day folic acid supplementation for 12 months in 77 Mild Cognitive Impairment patients, with improved cognitive function results (based on IQ Test and digit span test). In his study, Ma proved that consuming 400 µg folic acid supplementation for 12 months can reduce levels of IL-6, TNF-α, and Aβ-42 (β-amyloid). The presence of peripheral inflammation can cause changes in the hippocampus, including hippocampal volume. In addition, the hippocampus is also a receptor for large amounts of inflammatory cytokines, such as IL-6 and IL-1β. Thus, folic acid supplementation may potentially improve cognitive function by reducing peripheral inflammatory cytokine levels.

MoCA Ina consists of 30 points, which include several questions, grouped as follows: visual executive (7 points), naming (3 points), memory (5 points), attention (6 points), language (3 points), abstraction (2 points), and orientation (6 points). If the subject's education is ≤12 years, the total MoCA Ina score is added 1 point. Because the number of points varies for each domain, the researcher tried to analyze whether there was a relationship between differences in serum homocysteine levels and changes in cognitive function in nominal form, namely increased/unincreased serum homocysteine with improved/unimproved cognitive function. Based on the Chi square test with the nominal group division, changes in homocysteine levels had a significant difference in changes in cognitive function (p 0.018).

Pinar Oner *et al* (2023) found that homocysteine levels tended to be higher in post-COVID-19 patients compared to the control group, and higher homocysteine levels were significantly associated with decreased MoCA scores ($p < 0.001$, $r = -0.705$). This confirms that in inflammatory conditions, homocysteine levels will increase. In this study, an increase in homocysteine of 1 µmol/L was found to have a risk of decreasing the MoCA score by 0.765 points. Homocysteine is a neurotoxicant that can disrupt the integrity of the blood-brain barrier. In addition, homocysteine initiates the proinflammatory process and can cause neurological dysfunction through oxidative stress. Oxidative stress caused by homocysteine can be due to increased reactive oxygen species (ROS), inactivation of the nitric oxide synthase pathway, and lipid peroxidation, which are formed in the brain by blocking NMDA receptors.

Hyperhomocysteinemia is associated with thromboembolism and vascular damage. Thus, homocysteine can cause cognitive impairment through cerebrovascular events as well.[19]

A perfusional MRI study found that in normal individuals, hyperhomocysteinemia was associated with decreased cerebral blood flow, especially in the frontal and parietal cortex, which is not associated with other vascular risk factors. Simona Luzzi *et al*. (2021) examined the effect of homocysteine on cognitive function through several neuropsychological instruments. Hyperhomocysteine has a significant relationship with changes in performance in tasks involving memory and motor planning functions. The association of homocysteine with memory performance is thought to be due to the background that hyperhomocysteine is associated with more severe temporomedial lobe atrophy. The relationship between homocysteine and motor planning function (Luria) is still unclear, but is thought to be related to the frontal lobe.[20]

CONCLUSION

Folic acid supplementation does not affect changes in homocysteine levels (p 0.322). There is an effect of folic acid supplementation on changes in cognitive function in the elderly (p 0.000). There is an effect of changes in homocysteine levels (p 0.018) on changes in global cognitive function with r = 0.763 which shows a strong correlation.

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