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ASSOCIATION OF LIPID PROFILES AND COGNITIVE FUNCTION DETERIORATION OF GERIATRIC OUTPATIENTS AT NEUROLOGY CLINIC GUNUNGSITOLI REGIONAL GENERAL HOSPITAL

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ABSTRACT

Background: The increase of life expectancy in Indonesia causes increasing numbers of dementia, mostly caused by Alzheimer's disease (AD). High serum cholesterol level has been suggested as a risk factor for AD. The strongest evidence linking lipid profile with AD provided by previous experimental studies where adding or reducing cholesterol altered amyloid precursor protein (APP) and amyloid β-protein (Aβ) levels is the basic of this research.

Objective: To determine whether lipid profile is associated with cognitive function deterioration of geriatric outpatients at Neurology Clinic Gunungsitoli Regional General Hospital.

Methods: Participants of this cross-sectional study were outpatient geriatric patients at Neurology Clinic Gunungsitoli Regional General Hospital (n=85; mean age, 62.46±5.49 years old). The cognitive state was evaluated using Montreal Cognitive Assessment Indonesian Version (MoCA-INA) and those with MoCA-INA score <24 were considered cognitively declined. Concentrations of serum lipid profile were measured and correlated with cognitive state using Pearson's correlation. Multiple logistic regression analysis was used to calculate odds ratios (ORs) for cognitive decline.

Results: Based on Pearson's correlation test, high-density lipoprotein (HDL) level had significant strong positive correlation with MoCA-INA score (r=0.876;p=0.000) and triglyceride level had significant strong negative correlation with MoCA-INA score (r=-0.726;p=0.000). Relatively to cognitive decline, ORs for decreased HDL level was 3.19 (95%CI 2.02-4.36) and increased triglyceride level was 2.59 (95%CI 1.29-3.91).

Conclusion: There was a significant relationship between decreased HDL-cholesterol level and increased triglyceride level with cognitive decline in geriatric outpatients.

Key words: cognitive function in outpatients, geriatric, MoCA-INA, lipid profile

Background

The increase of life expectancy in Indonesia from 70.1 years in 2010-2015 period to 72.2 years in 2030-2035 period causes increasing number of dementia in Indonesia.[1,2] Most of the dementia case is caused by Alzheimer's disease.[2] Alzheimer's disease is a neurodegenerative disease causing a progressive decline in cognitive function in the form of episodic memory and other cortical functions as well as motor impairment in the later stages of this disease.[3] The Delphi Consensus in 2015 published 10% increase in the prevalence of dementia compared to previous publications in 2005.[3] Another research estimated 35,6 million people with dementia in 2010 with a doubling every 20 years to 65.7 million in 2030 and 115.4 million in 2050. In Southeast Asia the number of people with dementia is estimated to increase from 2.48 million in 2010 to 5.3 million in 2030.[4]

Increased total serum cholesterol level has been shown to increase the risk of developing Alzheimer's dementia.[5] An early study on cholesterol and dementia reported that the apolipoprotein E (apoE) genotype which played a role in the formation of amyloid β-protein (Aβ) plaque and Alzheimer's dementia depended on total cholesterol level, age, and patient sex.[6] Recent studies had also found that serum cholesterol level was approximately 10% higher in patients with Alzheimer's dementia compared to control subjects and this difference was statistically significant.[7] In a longitudinal study, cholesterol level was found to be significantly higher on the first measurement of patients with Alzheimer's dementia when compared with control subjects, but did not differ significantly on the second measurement from 11 to 26 years after the first measurement.[8] An odds ratio analysis using different models showed that cholesterol level in middle age significantly increased the risk for developing Alzheimer's dementia.[8] Meanwhile, another study reported that total serum cholesterol level was significantly higher in mild cognitive impairment (MCI) subjects compared to controls, but it was also observed that elevated serum triglyceride and serum high-density lipoprotein (HDL) level were significantly associated with the occurrence of MCI.[9] In contrast, there had also been studies reporting that serum low-density lipoprotein (LDL) level did not differ significantly in patients with Alzheimer's dementia compared to control subjects, but total cholesterol level was significantly lower in patients with Alzheimer's dementia compared to control subjects.[10]

There was no national research data on the prevalence of dementia in Indonesia. However, in line with the increasing population growth of elderly in Indonesia, there will also be increasing number of dementia cases. Dementia is a syndrome of decreased intellectual function compared to previous condition which is severe enough to interfere social and professional activities, which is reflected in dependence of the patient's daily life activities, usually changes in behavior, and is not caused by delirium or major psychiatric disorders.[3,11]

Purpose

Because of the high prevalence and level of dependence due to dementia, researchers were interested in conducting a study on the relationship between lipid profile and decreased cognitive function of geriatric outpatients at neurology clinic of Gunungsitoli Regional General Hospital, the only one referral hospital in Nias Island. This study is expected to be used as basis for determining the prognosis of cognitive decline in geriatric patients based on their lipid profile.

Method

This analytic observational research was conducted at neurology clinic and laboratory of Gunungsitoli Regional General Hospital from January to May 2020 with a cross sectional design. The research subjects were determined by consecutive sampling from geriatric outpatients of neurology clinic Gunungsitoli Regional General Hospital which met the inclusion and exclusion criteria until the analysis requirements was fulfilled. Research subjects who met the inclusion criteria signed a written informed consent and underwent history taking, lipid profile examination, and cognitive function test using MoCA-INA test. This study design was approved by the local institutional review board, Gunungsitoli Regional General Hospital Health Research Ethics Committee through ethical clearance number 800/7466/KEK

based on the letter of research recommendation from Badan Penelitian, Pengembangan, dan Perencanaan Daerah of Nias Regency number 050/612/Litbangrenc/Bappeda.

The inclusion criteria were geriatric outpatients (aged≥55 years old) of neurology clinic Gunungsitoli Regional General Hospital with frailty score≤9 based on the Edmonton Frailty Scale, agreed to take part in this research proven by signing an informed consent, cooperative, fully aware (compos mentis), and were able to read and write. While the exclusion criteria were patients with functional psychiatric disorders; history of using systemic psychotropic drugs and cholesterol-lowering drugs; history of narcotics, alcohol, psychotropic substances, and other additives abuse; suspicion of space-occupying lesion processes or brain tumors; transient ischemic attack (TIA); history of stroke, acute coronary syndrome, hypertension, and diabetes mellitus; history of education less than 6 years; and verbal communication difficulties using Indonesian language.

In this study, the lipid profile was the value obtained from laboratory examinations of the patient's blood in the form of serum HDL, LDL, triglycerides, and total cholesterol level carried out on the day the patient visited the neurology clinic of Gunungsitoli Regional General Hospital. Blood samples were drawn from each patient after fasting for 10-12 hours and immediately stored at 4°C. Serum was obtained on the same day by centrifugation of the sample at 3500 rpm for 10 minutes and stored at -30°C until biochemical analysis was performed. Researchers used Roche, Sigma, and Accurex reagents and kits in this study. The decline in cognitive function in the form of the MoCA-INA score was carried out on the day the patient visited the neurology clinic of Gunungsitoli Regional General Hospital. Patients with MoCA-INA score<24 were categorized as having decreased cognitive function.[3]

Furthermore, data collected from this study had been analyzed with multiple logistic regression test to determine the odds ratios (ORs) between the lipid profile and the decline in cognitive function of geriatric patients manifested in the form of MoCA-INA score. Data collected from this study which were normally distributed could also be analyzed using Pearson correlation test to determine the relationship between lipid profiles and decreased cognitive function in geriatric patients manifested in the form of MoCA-INA score. Results of Pearson correlation test were expressed in terms of contingency coefficient (r) measuring the direction and strength of the linear relationship between the two variables. All data analysis process was performed using SPSS Windows 22.0 program.

Result

The subjects of this study were 85 geriatric outpatients in neurology clinic of Gunungsitoli Regional General Hospital who met the inclusion and exclusion criteria, consisting of 40 men (47.06%) and 45 women (52.94%). The mean age of the study subjects was 62.46±5.49 years old with range of age from 56 to 79 years old.

Total cholesterol level of the study subjects ranged from 141–348 mg/dL with average of 217.85±47.39 mg/dL. Serum HDL level of the study subjects ranged from 32-59 mg/dL with average of 46.81±6.09 mg/dL. Serum LDL level of the study subjects ranged from 52-261 mg/dL with average of 136.87±41.33 mg/dL. The serum triglyceride level of the study subjects ranged from 80-426 mg/dL with average of 170.61±62.11 mg / dL.

Cognitive function was measured using MoCA-INA test instrument. On this examination, the results of MoCA-INA score range were between 19-30 with average of 23.82±2.87 as shown in Figure 1.

The result of One-Sample Kolmogorov-Smirnov test using SPSS 22.0 for Windows showed that all data were normally distributed (p>0.05). The correlation of lipid profile with MoCA-INA score reflecting the cognitive function of the study subjects was assessed by performing Pearson correlation test to determine the contingency coefficient. The test results showed a linear correlation with strong and statistically significant correlation strength on the examination of HDL cholesterol and triglyceride level as shown in Figure 2.

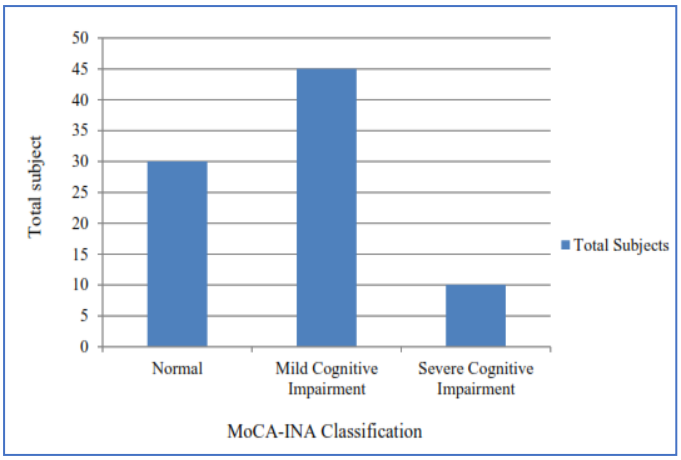

Figure 1. Results of MoCA-INA Score

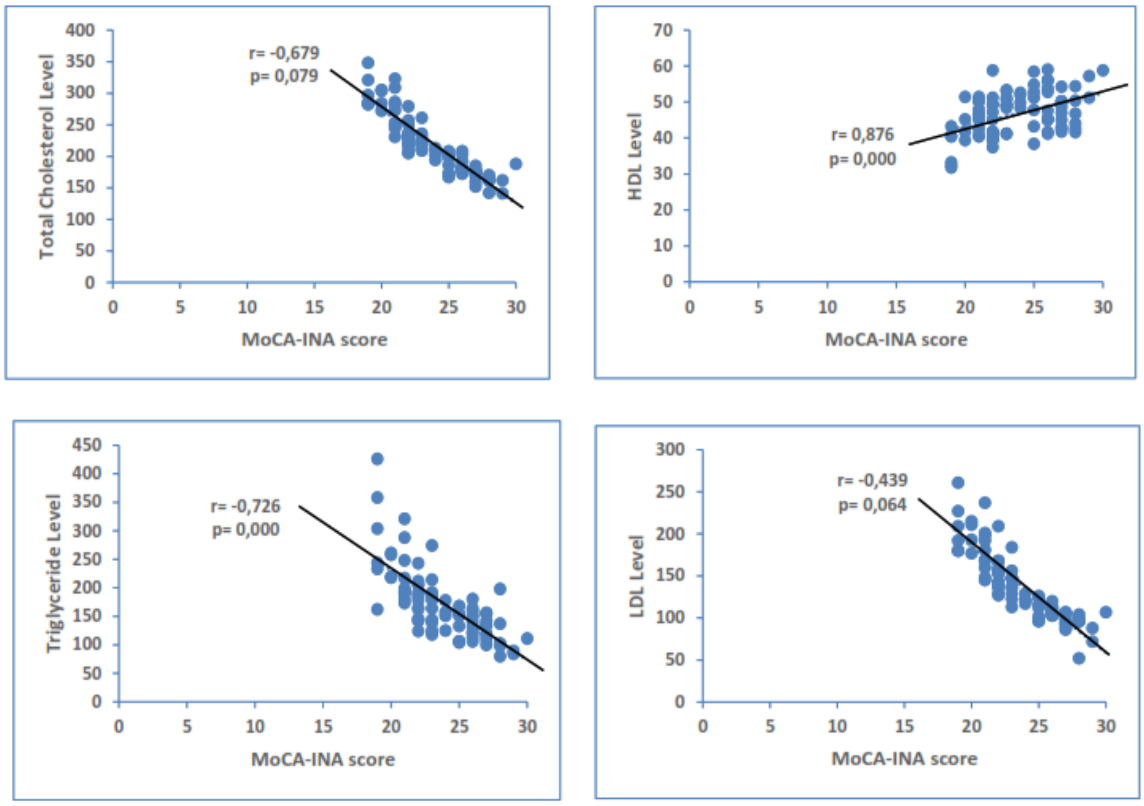

Figure 2. Correlation between Lipid Profile and MoCA-INA Score

Furthermore, the lipid profile data and MoCA-INA score from this study were also analyzed by performing multiple logistic regression tests to determine the ORs between lipid profile and cognitive decline as shown in Figure 3. The statistically significant multiple logistic regression test results showed ORs for decreased HDL cholesterol level on cognitive function was 3.19 (95%CI 2.02-4.36) and ORs for increased triglyceride level on cognitive function was 2.59 (95%CI 1.29-3.91). Meanwhile, ORs for increased total cholesterol level on cognitive function was 2.07 (95%CI 1.02-3.11) and ORs for increased LDL cholesterol level on cognitive function was 1.37 (95% CI 0.41- 2.34). However, both the ORs value for increased total cholesterol level and increased LDL cholesterol level were not statistically

significant as were their correlation to cognitive function.

In addition, researchers also obtained a correlation coefficient (R) of 0.772 and a coefficient of determination (R^2) of 0.752 with significance of p=0.000 from the multiple logistic regression test. This result showed that there was a close relationship between lipid profile and cognitive function, where the percentage effect of lipid profile on cognitive decline in this study was 75.2% and the remaining 24.8% was influenced by other factors, like genetic, race, sex, and nutrition.[8,10]

Discussion

This study showed a strong and statistically significant relationship between lower HDL level or higher triglyceride level and the incidence of cognitive impairment in geriatric patients. Total cholesterol level and LDL level did not show a statistically significant association with cognitive impairment in geriatric patients. Research from Dimopoulos et al. also mentioned a relationship between low HDL cholesterol level and high triglyceride level with memory problems and depression in elderly patient group.

Lipids and lipoproteins may have direct effect with neurodegenerative diseases. There are some mechanisms explaining the association between low HDL cholesterol level and cognitive impairment. HDL is lipoprotein found in plasma and cerebrospinal fluid. HDL contains apoE and facilitates the reverse transport of cholesterol, the transport of other types of cholesterol from various tissues (including the brain) to the liver. HDL enters the central nervous system via blood-brain barrier and involved in the regulation of metabolism of Aβ, a major constituent of amyloid plaque and its accumulation in the brain.[12,13]

Research from Exel et al. also supported a direct relationship between HDL and cognitive function through atherosclerosis mechanism. It had been shown that atherosclerosis was associated with clinical and subclinical ischemic processes in brain contributing to the development of dementia onset. Cerebrovascular changes and pathological changes in Alzheimer's disease often coincided in dementia case and could act synergistically in decreased cognitive function. At the same time low serum HDL concentration had been associated with an increased risk of stroke and patients suffering stroke had a higher risk of developing Alzheimer's disease.[14,15]

Another mechanism linking low HDL level to neuronal degeneration may be related to its role as an anti-inflammatory or antioxidant agent. The neuroprotective properties of HDL include accelerated maturation of synapses, maintenance of synaptic plasticity, increased Aβ catabolism, increased hippocampal volume, anti-inflammatory effects, and antioxidant effects. Oxidative stress including lipid peroxidation has been shown to be a mediator of the pathological effects of risk factors for Alzheimer's disease. Because HDL is a lipoprotein that is responsible for the processing of cholesterol efflux from brain cells, it is possible that HDL deficiency or dysfunction can lead to tauopathies or dysgenesis of the synaptic process, so that individuals with dyslipidemia may be more susceptible to neurodegenerative diseases.[15,16]

According to research from Aschenco et al., lifestyle interventions including a healthy diet, regular exercise, weight control, and smoking cessation had been shown to increase HDL level which also had neuroprotective effects.[16] In addition, HDL will be mediated by the activity of cholesterol ester transfer protein (CETP) which also associated with increased life expectancy, increased cognitive function, and dementia-free conditions.[13,16] HDL can suppress Aβ production by lowering cellular cholesterol through activation of cholesterol reverse transport mediated by ABC transporter. HDL can also directly bind excess Aβ to inhibit its oligomerization. Oligomerization is a major step in the transformation of toxic monomeric peptides into neurotoxic compounds that can cause memory loss.[17]

Meanwhile, research by Yin et al. showed that high triglyceride level was associated with risk of cognitive dysfunction.[18] Recent molecular studies had shown that decreased triglyceride level could increase the transport of ghrelin and insulin across the blood-brain barrier, which could have a positive effect on cognitive function.[19] However, increase in serum triglyceride level can trigger the emergence of orexigenic hypothalamic peptides which have negative effect on cognitive function. This mechanism makes triglyceride plays an important role in improving cognitive function.[20]

Another research from Schilling et al. stated that the triglyceride level circulating during fasting were in the form of very low-density lipoprotein (VLDL) which was synthesized by the liver using saturated fatty acids.[19] Therefore, higher triglyceride level indicates the amount of saturated fatty acids in abundance. Saturated fatty acids will increase the production of inflammatory cytokines. Studies had shown that high intake of saturated fatty acids could accelerate cognitive decline or increase the risk of dementia.[18]

Cholesterol actually plays an important role in the maintenance of the lipid bilayer of cell membranes (lipid rafts). Changes in total cholesterol level can affect cell membrane function which may interfere with synaptic transmission in some neurotransmitter systems. Research by Chrichton et al. had shown an association between changes in serum cholesterol level and the 5-hydroxytryptamine (5-HT) system.[21] A 5-HT system deficit can manifest in some events of mood or appetite regulation disorders and has potential to affect cognitive function through impaired transmission of the frontal lobe. Based on the important role of lipid in cell maintenance, cholesterol plays an important role in brain development and function. Fatty acids that make up cholesterol are important molecular components that determine the integrity and performance of the brain, so maintained fatty acid level are essential for good brain function.[20] In addition, unsaturated fatty acids can reduce the production of inflammatory cytokines or decrease tissue response. Research had shown that high intake of unsaturated fatty acids could protect cognitive function or reduce the risk of dementia.[18] Cholesterol is very important in myelination and formation of synapses and dendrites. Very low cholesterol level can also have an adverse effect on brain, especially during its development period.[21,22] In this study, the relationship between increased total cholesterol level and cognitive function was not statistically significant. This result is in line with the research of Elias et al. which stated that very low cholesterol level and impaired cognitive function was closely related to the need of total cholesterol for metabolic processes of nerve cells. The interaction between plasma cholesterol level, cholesterol contained in cell membranes, and very complex serotonergic activity may explain the negative effect of very low total cholesterol level on cognitive function.[23] Although the cholesterol-serotonin hypothesis had been developed to explain the relationship between very low total cholesterol level, violent behavior, and suicide, it is possible that the adverse modulation effects of low total cholesterol level on serotonergic activity may result in the role of serotonin in cognitive function.[23]

Meanwhile, research by Oliveira et al. stated that high total cholesterol level which usually occurred in conjunction with chronic disease, metabolic syndrome, poor nutritional intake, and malignancy could ultimately be associated with poor cognitive function.[24] These many other components and comorbid factors affecting the increase of total cholesterol level might also cause the result of analysis about relationship between total cholesterol level and cognitive function was statistically insignificant.

In this study, it was also found that the relationship between increased LDL cholesterol level and cognitive function was not statistically significant. The pathophysiological mechanism of high LDL level in causing dementia in geriatric patients is still unclear, but the study of Anstey et al. mentioned that there was a possible relationship between the carotid artery atherosclerosis process and cognitive decline through cerebral embolism or hypoperfusion mediated by higher LDL level.[25] In addition, Reitz et al. stated that lipid peroxidase which might be a major pro-inflammatory factor in the aging process and hypercholesterolemic conditions could cause microglia activation and beta Aβ plaque deposits.[26] In contrast, study of Ma et al. found that restricting diet rich in LDL cholesterol could reduce the susceptibility of the brain to acute injury such as stroke and the possibility of age-related retardation of cognitive function.[27] Thus, oxidation of LDL cholesterol in brain may be more relevant to the pathogenesis of dementia cases. vascular dementia, or dementia with mixed pathology (Alzheimer's disease co-occurring with stroke). This argument is also supported by research from Ma et al. which stated that the relationship between LDL cholesterol level and decreased cognitive function was statistically significant in post hemorrhagic stroke patients.[27]

In this study, comorbid diseases such as stroke, hypertension, and diabetes mellitus which might be confounding factors and affect laboratory values were excluded. As research by Dimopoulos et al. stated that education level was inversely correlated with dementia risk and observed existing references from the Perhimpunan Dokter Spesialis Saraf Indonesia (PERDOSSI), researchers also attempted to exclude respondents who had history of formal education less than six years and could not communicate verbally using Indonesian, so the research data would be homogeneous.[3,12]

This study was a cross-sectional analysis involving only one clinical evaluation and one individual lipid profile examination without further follow-up. Dynamic changes in cholesterol level over time could not be considered in this study, making it difficult for researchers to distinguish either changes in lipid profile preceded cognitive impairment or changes in lipid profile developed during the course of cognitive impairment. Another limitation of this study was the absence of confirmed apoE4 genotype data as risk factor for Alzheimer's dementia.[10,16]

Finally, the findings of this study supported the potential benefit of measuring lipid profiles as biomarkers in the prevention of dementia in geriatrics and provided an indication for further research in the future. Apart from the need of dementia treatment options, there is actually an urgent need for the discovery of new biomarkers of early dementia as well as biomarkers for monitoring the severity of dementia which may also be useful as new dementia treatment targets. In addition, the condition of the geriatric patients involved in this study was quite healthy, as seen from the exclusion criteria that included degenerative diseases (such as acute coronary syndrome, hypertension, and diabetes mellitus), but the samples obtained were quite large. This finding was an interesting aspect and could be a topic for further research.

Conclusion

There was a significant relationship between HDL cholesterol level and triglyceride level with decreased cognitive function of geriatric outpatients.

Acknowledgment

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Conflict of Interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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