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Research Article

Correlation between Atherogenic Index of Plasma and Various Domains of Cognitive Function in Type 2 Diabetes Mellitus Patients

Korelasi Atherogenic *Index of Plasma* dengan Berbagai Domain Fungsi Kognitif pada Pasien Diabetes Melitus Tipe 2

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ABSTRACT

Cognitive impairment in patients with Type 2 Diabetes Mellitus (T2DM) is related to the lack of blood supply to the brain. Previous studies showed that the atherogenic index of plasma (AIP) is a predictor of vascular abnormalities, but studies investigating its association with cognitive functions in T2DM patients younger than 60 years remain limited. This study aimed to determine the correlation between AIP and various domains of cognitive function in T2DM patients. This study was a cross-sectional study involving 75 T2DM patients selected using a consecutive sampling technique at Haji Adam Malik General Hospital Medan from July 2021 to January 2022. Cognitive function was examined using the Visual Cognitive Assessment Test Indonesian Version (VCAT-INA) on several cognition domains. The AIP value of each patient was measured and categorized into high (AIP>0.21), intermediate (AIP between >0.11 and ≤0.21), or low (≤0.11). The mean triglyceride level was 176±108.3mg/dl, the HDL-C level was 38.3±12.1mg/dl, and the mean AIP value was 0.191±0.25. The mean score of the VCAT-INA was 21.7±2.3, which was lower than normal. The AIP value showed significant negative correlation with global cognition (r=0.432, p<0.001) and various cognitive domains, namely memory (r=-0.375, p=0.001), attention (r=-0.383, p=0.001), executive function (r=-0.051, p=0.663), visuospatial (r=-0.306, p=0.008), and language (r=-0.352, p=0.002). In short, there is a significant correlation between AIP value and domains of cognitive function, such as memory, attention, visuospatial, and language domains, but not with executive domains.

Keywords: *Atherogenic index of plasma, cognitive, diabetes mellitus*

ABSTRAK

Gangguan kognitif pada pasien dengan Diabetes Mellitus Tipe 2 (DMT2) terkait dengan kurangnya suplai darah ke otak. Studi sebelumnya membuktikan bahwa *atherogenic index of plasma* (AIP) merupakan prediktor kelainan pembuluh darah yang baik namun, studi yang menyelidiki hubungannya dengan kognisi pada pasien T2DM yang lebih muda dari 60 tahun masih terbatas. Tujuan penelitian ini adalah untuk mengetahui korelasi antara AIP dengan berbagai domain fungsi kognitif pada pasien DMT2. Penelitian ini merupakan penelitian *cross sectional* yang melibatkan 75 pasien DMT2 yang dipilih menggunakan teknik consecutive sampling, di Rumah Sakit Umum Haji Adam Malik Medan dari Juli 2021 hingga Januari 2022. Fungsi kognitif diperiksa menggunakan *Visual Cognitive Assessment Test Indonesian Version* (VCAT-INA) yang menilai beberapa domain kognisi. Kadar kolesterol nilai AIP dihitung untuk setiap pasien, yang dikelompokkan menjadi 3 kategori yang tinggi (AIP>0,21); menengah (AIP>0,11dan ≤0,21) dan rendah (≤0,11). Rerata kadar trigliserida adalah 176±108,3mg/dl, HDL-C (38,3±12,1mg/dl), dan nilai AIP (0,191±0,25). Rerata skor VCAT-INA adalah 21,7±2,3, yang lebih rendah dari nilai normal. Nilai AIP menunjukkan korelasi negatif yang signifikan dengan kognisi global (r=-0,432, p<0,001) dan berbagai domain kognitif, yaitu memori (r=- 0,375, p=0,001), atensi (r=-0,383, p=0,001), fungsi eksekutif (r=-0,051, p=0,663), visuospatial (r=-0,306, p=0,008), dan bahasa (r=-0,352, p=0,002). Dapat disimpulkan ada hubungan yang signifikan antara nilai AIP dengan domain fungsi kognitif seperti memori, atensi, visuospatial, dan domain bahasa tetapi tidak dengan domain eksekutif.

Kata Kunci: *Atherogenic index of plasma*, diabetes melitus, kognitif

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INTRODUCTION

One of the major complications of Type 2 Diabetes Mellitus (T2DM) is cognitive impairment. The high risk of vascular dysfunction in T2DM is believed to cause disturbances in various domains of cognitive function. Dyslipidemia is known to accelerate cognitive impairment due to the denaturation of neurons responsible for cognitive function and the development of atherosclerosis (1).

Some of the major lipid fraction abnormalities are increased total cholesterol, LDL cholesterol (LDL-C), triglycerides (TG), and a decrease in HDL cholesterol (HDL-C). These changes in lipid profiles are interrelated and cannot be viewed separately (2). Recently, LDL particle size has been recognized to be highly varied, and the differences in LDL particle size affect the risk of cardiovascular disease (3). Within the arterial wall, LDL will easily undergo oxidation, form foam cells, and ultimately form arteriosclerotic plaques (3). Several studies have shown the index assessment in the form of the triglyceride/HDL-C ratio (TG/HDL-C), which is a good predictor of cardiovascular disease. It is because the ratio of TG/HDL-C can describe LDL particle size (4). A high ratio of TG/HDL-C describes that small and dense LDL particles are more easily oxidized to Ox-LDL (5).

Unstable arteriosclerotic plaques contain more macrophages and Ox-LDL than stable arteriosclerotic plaques. The measurement of LDL-C particles using Nuclear Magnetic Resonance (NMR) has been proven to better predict cardiovascular risk than LDL-C assessment (6). The logarithm of the ratio of TG to HDL-C is associated with LDL-C and HDL-C particle sizes. Measuring the particle size of LDL-C and HDL-C is difficult, but the calculation of the atherogenic index of plasma (AIP), which is the logarithmic ratio of molar concentrations of triglycerides divided by serum HDL-C, provides an overview of the particle size of LDL-C and HDL-C and is sensitive in predicting coronary heart diseases and cardiovascular diseases. Previous studies showed that AIP did not only reflect the true relationship between protective and atherogenic lipoprotein but also acted as a strong predictor of atherosclerosis and coronary heart disease (7).

Cognitive impairment, both MCI and dementia, can affect one or more cognitive domains, such as attention, language, memory, visuospatial, or executive function. Mild cognitive impairment, which is a transitional stage between normal aging and dementia, is more commonly observed in T2DM patients than in the general population. This findings were seen in older adults, while similar conditions among younger T2DM patients have not been extensively studied (8). Therefore, this study aimed to determine the correlation between the AIP and various domains of cognitive function in T2DM patients under 60 years of age.

METHODS

Study Design and Participants

This study was a descriptive-analytic cross-sectional study on data of T2DM patients at the Endocrinology Clinic, Haji Adam Malik General Hospital Medan. Grouping of participants was determined using a consecutive non-random sampling method. This study involved T2DM patients aged 60 years or younger who were able to speak Indonesian, cooperative, literate, and willing to give consent to participate in the study. Patients who were medically unstable (delirium), had psychiatric disorders or aphasia, experienced brain lesions (stroke, brain tumor, brain infection, and head trauma), and received statin treatment for the last three months were excluded from this study. Written informed consent was obtained from each participant.

Laboratory Assessment

Each patient underwent a laboratory assessment for lipid profile after eight hours of fasting. Since the atherogenic index of plasma is based on TG and HDL-C levels, the AIP value of each patient was then calculated based on the lipid profile levels and the logarithm (TG/HDL-C). The AIP values were then classified as low risk (≤0.11), medium/moderate risk (between >0.11 and ≤0.21), and high risk of cognitive impairment (>0.21) (7).

Cognitive Assessment

Cognitive function assessment was carried out using the Visual Cognitive Assessment Test (VCAT). This method is a visual-based tool suitable for a multilingual population with a normal score of 23-30, an MCI score of 18-22, and a dementia score of less than 18 (10). Its diagnostic performance and discriminative validities are superior compared to Mini-Mental State Examination (MMSE) and equal to Montreal Cognitive Assessment (MoCA) (10,11). The VCAT has been validated in four southeast Asian countries, including Indonesia. The VCAT method effectively differentiates between healthy control and subjects with cognitive impairment (MCI and mild dementia) (12). As a visual-based test, VCAT-INA can be applied as a cognitive screening tool in daily clinical practice without a significant language barrier (11).

The VCAT evaluated memory, executive function, visuospatial function, attention, and semantic knowledge. The test items for each cognitive domain were visual-based. The episodic memory domain consisted of seven test items assessing immediate and delayed recall using scenarios, shapes, and objects. The executive function domain consist of four items to evaluate pattern recognition-completion, gear movement mechanism, and picture grouping based on categories. The visuospatial function domain contained two items assessing visuospatial abilities via cube reconstruction, visual depth perception, and grid navigation. The language domain used two items, and participants were required to name pictures. The semantic fluency was assessed using four categories, which were countries, vegetables, modes of transport, and kitchen utensils. A symbol recognition cancellation task was used to assess the attention domain (9).

Statistical Analysis

Data from the study were statistically analyzed using the Statistical Product and Science Service (SPSS). The correlation between the AIP ratio and cognitive function domains (memory, attention, executive, visuospatial, and language) was analyzed using the Spearman correlation test.

RESULTS

Seventy five T2DM patients were involved in this study. Most patients were male (39 patients, 52%), in the 51-60 years age group (48 patients, 64%), and had up to 12 years

of education (49 patients, 65.3%).

The VCAT-INA assessment results showed that the lowest score was 16, and the highest was 26, with a mean VCAT-INA score of 21.7±2.3. Based on the VCAT-INA score, 47 patients (62.7%) had MCI, 26 patients (34.7%) were normal, and only 2 patients (2.7%) suffered from dementia.

The mean level of triglyceride was 176±108.3 mg/dL, with the lowest level of 57 mg/dL and the highest level of 623 mg/dL. The mean HDL level was 38.3±12.1 mg/dL, with the lowest level of 12 mg/dL and the highest level of 75 mg/dL. The mean AIP ratio was 0.19±0.25 mg/dL, with the lowest value of -0.36 and the highest value of 1.003. The complete characteristics of the patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of patients

Demographic Characteristics	n = 75 (%)
Sex, n (%)	
Male	39 (52.0)
Female	36 (48.0)
Age, year	
Mean±SD	51.5±5.9
Median (Min-Max)	53 (36-59)
Age groups, n (%)	
31 – 40 years	4 (5.3)
41 – 50 years	23 (30.7)
51 – 60 years	48 (64.0)
Ethnicity, n (%)	
Acehnese	4 (5.3)
Batak	56 (74.7)
Javanese	11 (14.7)
Malay	4 (5.3)
Education, n (%)	
Primary School (up to 6 years)	2 (2.7)
Junior High School (7-9 years)	3 (4.0)
Senior High School (10-12 years)	49 (65.3)
More than 12 years	21 (28.0)
Occupation, n (%)	
Housewife	15 (20.0)
Farmer	9 (12.0)
General Employee	6 (8.0)
Civil Servants	27 (36.0)
Self-Employee	17 (22.7)
National Army	1 (1.3)
VCAT-INA Score	
Mean±SD	21.7±2.3
Median (Min-Max)	22 (16 – 26)
VCAT-INA Classification	
Normal (23 - 30)	26 (34.7)
MCI (18 - 22)	47 (62.7)
Dementia (0 - 17)	2 (2.7)
Lipid Profile	
Triglyceride, mg/dL	
Mean±SD	176±108.3
Median (Min-Max)	154(57 – 623)
HDL, mg/dL	
Mean±SD	38.3±12.1
Median (Min-Max)	37(12 – 75)
AIP Ratio	
Mean±SD	0.191±0.250
Median (Min-Max)	0.23 ((-0.36) – 1.003)

Table 2 presents the demographic characteristics of the patients based on cognitive function, namely normal, MCI, and dementia. There was no difference in the demographic characteristics of the patients in the three groups (p>0.05). The highest AIP value was found in the group of patients with dementia (0.43±0.34), while the lowest AIP value was found in the group of cognitively normal patients (0.029±0.21). There was a significant difference in the AIP values based on cognitive function (p<0.001).

The Spearman correlation test showed a significant negative correlation between the AIP value and the total VCAT-INA score (r=-0.432, p=0.001). However, there were significant correlations between the AIP value and several domains of cognitive function, which were memory r=-0.375 (p=0.001), attention r=-0.383 (p<0.001), visuospatial r=-0.306 (p=0.008), and language r=-0.352 (p=0.002), while the executive domain did not have a significant relationship with correlation r=-0.051(p= 0.663). The correlation test results between the AIP ratio and the cognitive function domain with the VCAT-INA score are presented in Table 3.

Table 3. Correlation of AIP Ratio to cognitive function (VCAT-INA Score) and domain of cognitive function

	AIP Ratio
Cognitive Function (VCAT-INA)	r = -0.432
	p = 0.000
Memory Domain	r = - 0.375
	p = 0.001
Attention Domain	r = -0.383
	p = 0.001
Executive Domain	r = -0.051
	p = 0.663
Visuospatial Domain	r = -0.306
	p = 0.008
Language Domain	r = - 0.352
	p = 0.002

DISCUSSION

The pathological process of dementia occurs several years before the clinical picture becomes clear. The transitional phase of cognitive impairment between the normal aging process and the onset of dementia is known as MCI. Early detection to assess MCI is vital for taking preventive measures to impede dementia. Preventive measures should be taken since delaying the onset of dementia by five years can reduce the incidence of dementia by half. Therefore, it is necessary to know the risk factors contributing to cognitive impairment, especially in a high-risk population, such as T2DM patients.

This study was conducted on patients younger than 60 years old, reflected that old age was associated with worse cognitive function. The age factor has been widely studied and is a risk factor for dementia. The risk of dementia doubles every five years in individuals over 65 years old, and 50% of individuals over 85 years old suffer from dementia (13). In a study by Heug *et al.,* the mean age for dementia was 73.8±3.4 years (14).

From this study, based on the VCAT-Ina score, patients with impaired cognitive function showed higher AIP values than patients with normal cognition. There were moderate and negative correlations, meaning that an increase in the AIP ratio value would be followed by a decrease in the VCAT-INA score. The risk of decreased cognitive function

Table 2 Demographic characteristics of research patients based on cognitive function with VCAT-INA Score

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Demographic Characteristics	Cognitive Function			p
	Normal n=26	MCI n=47	Dementia n=2	
Sex, n (%)				
Man	10 (13.3)	28 (37.3)	1 (1.3)	0.101[b]
Woman	16 (21.3)	19 (25.3)	1 (1.3)	
Age, year				
Mean±SD	52.2±5.3	50.9±6.2	57±1.4	0.252[b]
Min-Max	41 – 59	36 - 59	56 - 58	
Age, n (%)				
31 - 40 years	0	4	0	0.289[b]
41 - 50 years	9	14	0	
51 - 60 years	17	29	2	
Ethnic, n (%)				
Acehnese	3	1	0	0.076[b]
Batak	20	35	1	
Javanese	3	8	0	
Malay	0	3	1	
Education, n (%)				
Primary School	0	2	0	0.372[b]
Junior High School	1	2	0	
Senior High School	15	32	2	
Bachelor Degree	10	11	0	
Occupation, n (%)				
Housewife	3	11	1	0.053[b]
Farmer	1	8	0	
General Employee	3	3	0	
Civil Servants	14	13	0	
Self-Employee	4	12	1	
National Army	1	0	0	
Lipid Profile				
Triglyceride, mg/dL				
Mean±SD	109.92±38.78	211.51±119	204±56.56	0.000[b]
Min - c Max	94-125	176-246	164-244	
HDL-C, mg/dL				
Mean±SD	44.8±13.3	34.8±9.8	35.0±16.9	0.003[b]
Min - Max	15 - 75	12 - 60	23 - 47	
AIP Ratio				
Mean±SD	0.029±0.21	0.38±0.26	0.43±0.34	0.000[b]
Min - Max	- 0.368 – 0.4	- 0.19 – 1.003	0.183 – 0.666	
VCAT-INA				
Mean±SD	24.2±1.2	20.5±1.3	16.5±0.7	0.000[b]
Median (min-max)	24(22-26)	21(18-22)	16.5(16-17)	

Note: [a]Mann Whitney, [b]Kruskal Wallis

increases in conditions of increased AIP ratio. It is in line with the risk of cerebral artery atherosclerosis, one of the mechanisms of cognitive decline, where a high AIP ratio can trigger atherosclerosis. The correlation analysis results of the AIP ratio and each cognitive function domain using the VCAT-INA score showed a significant relationship between the AIP value and memory, attention, visuospatial, and language domains, but not the executive domain.

The mechanism of plasma lipids' influence on cognitive function is a complex issue and has not been fully understood. Research to identify the effect of plasma lipid concentration on cognitive impairment is important to provide insight into their correlation. This is also needed to develop new strategies in the prevention and treatment field (15).

One of the parameters to predict the presence of vascular abnormalities is the AIP value, which is a logarithm of serum triglycerides/serum HDL-C. The AIP value will increase in conditions of increased serum triglyceride levels followed by a decrease in HDL-C levels in the blood. The higher the AIP value, the higher the risk of cardiovascular diseases, including stroke and impaired cognitive function (7).

The results of this study showed that patients with cognitive impairment, according to the VCAT-INA, had abnormal mean HDL levels, while patients without cognitive impairment had normal HDL levels (16). It indicates that in addition to CVD prevention, increasing HDL-C levels is a good strategy to prevent dementia because HDL can inhibit beta-amyloid aggregation and promote amyloid removal (17). A decrease in HDL-C after middle age is strongly associated with a significant increase in dementia later in life (18). HDL-C is an independent risk marker of cognitive decline in older age (19).

This study also found that patients with cognitive impairment, according to the VCAT-INA, had a high or abnormal mean triglyceride level (≥150mg/dl) (16). Individuals with risk of cardiovascular disease is prone to immediate, short-delay, and long-delay recall impairment associated with high triglyceride level. Higher triglyceride levels have been associated with decreased verbal learning (20). Besides, high triglyceride level is associated with poor performance on verbal tests (21). A major contributor to

decreased leptin transport across the blood-brain barrier (BBB) is triglycerides, which result in a relative decrease in brain leptin levels. Leptin stimulates AMP-activated protein kinase in the hippocampus, which is associated with a memory-enhancing effect. Triglyceride level is important cause of leptin resistance mediated by impaired transport across the BBB. It also evolves as a mechanism for the anorectic effect on leptin by increasing leptin transport across the BBB (22,23). Feinkohl *et al.*, concluded that lower HDL-C and high TG were associated with cognitive impairment, defined as a decrease in cognitive performance relative to the total sample (24).

A decreasing function of cognition domains in T2DM patients can be caused by the disruption of blood circulation to the brain. This is a result of the atherosclerosis process of the cerebral arteries, which causes reduction in the volume of the brain white matter that serves to connect the centers of information and analysis. In addition, there is also a reduction in the volume of grey matter, which is responsible for the patient's language skills and memory. Gray matter serves as the center of information processing (25).

This study proves that the risk of decreasing cognitive function is higher among T2DM patients with increasing AIP value. A high AIP value indicates a high triglyceride level and a low HDL level. Therefore, controlling blood sugar and triglyceride and HDL-C levels is necessary to prevent cognitive dysfunction in T2DM patients. Several other factors that can affect cognitive function in T2DM patients, such as diseases suffered by the subject, socioeconomic factors, and stress factors, are not analyzed, and became the limitation of this study.

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