ORIGINAL ARTICLE

Title

The Role of Methylglyoxal Accumulation on Cognitive Function Impairment of Chronic Hemodialysis Patients: an Observational Study

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Abstract

Background: Cognitive function decline is prevalent on routine hemodialysis patients. Many factors contribute to the increased risk of cognitive function impairment, one of them is the accumulation of uremic toxins. Methylglyoxal (MG) has been identified as one of the uremic toxins found in dialysis patients by the European Uremic Toxin Group. It has also been found much higher on CKD patients; over five times higher in non-dialysis CKD and 18-40 times higher in CKD patients on dialysis, and cause impaired cognitive function in rats with diabetes.

Aim: To find the correlation between blood MG levels and cognitive function of patients who underwent routine hemodialysis.

Methods: This study is an observational cross-sectional study done in Hemodialysis Unit of Dr. M Djamil General Hospital, Padang, West Sumatera, Indonesia. Fifty-seven subjects aged 40-60 years old were included in this study, where the blood MG levels were obtained. Cognitive function was measured using the Mini Mental State Examination (MMSE) questionnaire.

Result: Among 57 subjects, 29 (50.8%) were male, and 33 (57.9%) were 50-60 years old. The subjects' mean methylglyoxal levels were 10.8 (SD ± 3.2) µmol/L. The subjects' mean MMSE score was 26 (SD ± 1.8), with 35% of the subjects had low (<25) scores. Spearman correlation analysis showed a statistically significant negative correlation between methylglyoxal level and MMSE score ($r = -0.6$, $p < 0.001$).

Conclusion: High levels of methylglyoxal negatively correlates with cognitive function in chronic hemodialysis patients. Future research should include analysis regarding age, gender, hypertension, and other confounding factors.

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BACKGROUND

Chronic kidney disease (CKD) remains a health burden worldwide. According to data from WHO, this disease climbed its way from being number 27 of the world's biggest health burden worldwide in 1999 to number 18 in 2010.[1,2] Indonesian Renal Registry (IRR) reported the number of CKD patients in Indonesia went from 15,535 in 2011 to 19,621 in 2012.[3]In West Sumatera, the number of CKD patients was reported to be 199 by the end of 2012.[3] Cognitive function decline is prevalent in these patients, which can lead to increased mortality and reduced quality of life. Patients undergoing dialysis have 16-38% risk of cognitive impairment, higher than the 6.6% risk in general population.[4,5,6,7,8]Studies by Murray et al and Fadili et al also show 25-37% dialysis patients have cognitive impairment measured by Mini Mental State Examination (MMSE).[9,10]

Multiple mechanisms have been suggested to be the cause of this impairment, such as vascular abnormalities and accumulation of uremic toxins in CKD.[11,12,13]In 2013, the European Uremic Toxin Work Group found over 90 uremic toxin groups in dialysis patients, one of them is methylglyoxal (MG).[11,12]MG has been associated with cognitive decline in studies involving diabetic rats, for it will

react to lysine and arginine, forming advanced glycation end products (AGE) that can cause neuronal apoptosis.[14] The level of MG in CKD patients increases with the progression of CKD due to reduced excretion by the kidneys. A study in 2011 showed an increase of 1 unit of MG is correlated with a 0.36 decrease in MMSE score.[15]Based on the above data, this study aimed to find the correlation between methylglyoxal and changes in cognitive function of CKD patients who underwent routine HD in order to provide input in evaluating cognitive impairment in CKD patients. The result will help improve the patients' quality of life.

METHODS

This study was conducted in the Hemodialysis Unit in Dr. M. Djamil General Hospital, Padang, West Sumatra, from December 2015 to April 2016. The subjects were hemodialysis patients who had underwent routine dialysis for at least 3 months, aged 40-60 years old, and with a minimum educational degree of high school diploma or equivalent. Exclusion criteria were cerebrovascular disease, communication barrier such as mutism, aphasia, or decreased consciousness, and psychiatric disorders.

Using the appropriate formula, nine samples were needed. However, due to several variables that will influence the research, adjustments are made based on the table for linear regression analysis, adding a sample of 48 people so that the total sample in this study was 57. Samples were taken consecutively.

The study population was CKD patients and samples were CKD patients who met the inclusion and exclusion criteria. The data obtained from this study includes demographic characteristics such as gender, age (divided into two groups: 40-50 years old and 51-60 years old), educational level, systolic and diastolic blood pressure, hemoglobin level, fasting and post-prandial blood glucose, blood urea and creatinine level, cognitive impairment using Mini Mental Examination Score (MMSE), and MG level. MG was measured from subjects' blood using ELISA technique, with normal value 0.06-0.13 µmol/L. This study has been approved by the local ethical committee and all subjects have given written informed consent prior to this study.

RESULTS

Table 1 shows the characteristics of the subjects; 50.88% were male and 57.9% were in the age group of 51-60 years old, with the mean age of 51.4 (±6.7) years old. The subjects' level of education were 42.1% high school diploma, 36.8% associate degree (D3), and 33% bachelor degree or higher. The subjects' mean systolic blood pressure was 149.29 mmHg, whereas the subjects' mean diastolic blood pressure was 85.43 mmHg, both above the cutoff point for normal blood pressure. The mean value of both fasting and post-prandial blood glucose were

Table 1. Subjects' baseline characteristics

Baseline Characteristics	N (%)	Mean (±SD)
Gender		
Male	29 (50.88)	
Female	28 (49.18)	
Age (years)		51.40 (6.7)
40 – 50	24 (42.1)	
51 – 60	33 (57.9)	
Level of education		
High school diploma	24 (42.1)	
Associate degree	21 (36.8)	
Bachelor degree or higher	12 (21.1)	
Systolic blood pressure (mmHg)	57 (100)	149.29 (2.3)
Diastolic blood pressure (mmHg)	57 (100)	85.43 (1.3)
Hemoglobin (g/dl)	57 (100)	9.1 (1.3)
Fasting blood glucose (mg/dl)	57 (100)	121.1 (30.5)
Post-prandial blood glucose (mg/dl)	57 (100)	163.1 (42.4)
Blood urea (mg/dl)	57 (100)	132.46 (117.3)
Creatinine (mg/dl)	57 (100)	7.06 (1.7)

Table 2. Correlation between MG and MMSE score

Clinical Parameter	Mean	p-value	correlation coefficient (r)
Methylglyoxal (µmol/L)	10.8 (±3.2)	< 0.001	- 0.60
MMSE score	26 (22 – 29)		

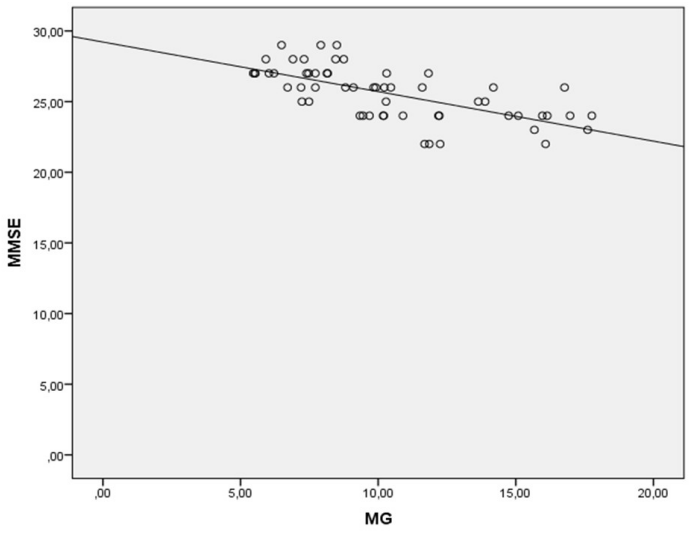

Figure 1. Correlation between MG (methylglyoxal levels) and MMSE score (r=-0,6; p<0,001)

121.1 (±30.5) g/dl and 163.1 (±42.2) g/dl, respectively. The MG level of the subjects was not normally distributed, with the mean value of 10 (± 3.2) µmol/L is significantly higher than normal levels of 0.06 – 0.13 µmol/L. The mean hemoglobin level of the subjects was 9.1 (±1.3) g/dl, nearing the lowest value of the recommended hemoglobin level in dialysis patients. The mean MMSE score of the subjects was 26, with the lowest score being 22 and the highest was 29. Thirty-five percent of the subjects have cognitive impairment (MMSE score <25). The Spearman correlation test was used to analyze the two variables with the result of a strong negative correlation between MG levels and MMSE score ($p<0.01$, $r=-0.6$) (Table 2).

DISCUSSION

Methylglyoxal is a dicarbonyl substance, a main metabolic product of glycolysis through triphosphate fragmentation pathway, mediated by dihydroxyacetone phosphates (DHAP). Other methylglyoxal sources are from fat and protein metabolism. The formed methylglyoxal will be degraded to lactic acid via the glyoxalase pathway which consists of 2 main enzymes namely glyoxalase I and glyoxalase II.[16,17]There are multiple mechanisms of cognitive impairment due to MG accumulation. MG itself can cause irreversible damage through aggregation and apoptosis of neurons.[18] MG is also a potent glycation agent; increased level of MG due to impaired excretion by the kidneys will increase its reaction with nucleic acid, lysine, and arginine.[16,17]This will result in increased level of the advanced glycation end product (AGE) such as argpyrimidine, hydroimidazole MG-H1, and MG derived lysine dimer. AGEs will then bind to their receptor (RAGE), and induce inflammatory reaction and neuronal apoptosis. MG and its AGEs are also inducers of reactive oxygen species (ROS), and thus causing cell aging.[16,17]The level of MG has been known to increase in certain diseases; it increased up to 1.3 times higher in diabetic patients, and up to 40 times higher in CKD patients compared to the general population.[19] Previous studies have shown an increased level of MG between 0.25 – 0.75 µmol/L can significantly cause neuronal damage.[16,20,21]In this study, the mean level of MG were almost 10 times higher than the cutoff point of normal MG level, consistent with current evidence available.

Cognitive function consists of attention, memory, visuospatial, language, and executive function such as planning, controlling, and evaluating.[22] Cognitive impairment consists of dysfunction in at least two components of cognitive function.[22]Based on MMSE score, the severity of cognitive impairment is divided into three groups: mild (20-24), moderate (13-20), and severe (<12).[23]Tests on the MMSE questionnaire include orientation tests, to assess awareness and memory, and registration test to assess working memory. A recall test was done to assess immediate memory, where the patient was told to recall three objects that had been proposed in the registration test. A decrease in concentration can occur if there is a disturbance in the attention test and calculation. This condition is found in diffuse degeneration or metabolic disorders. For the language tests, patients are asked to name objects pointed by the examiner; if patients were unable to name objects properly, a focal lesion in the brain or diffuse hemisphere dysfunction should be considered. Patients were asked to repeat a sentence; a repetition disorder indicates a disturbance in the perisylvian left hemisphere. Another test is to have the patient perform three gradual commands (comprehensive language). A disruption in this test indicates dysfunction of the left posterior temporal lobe or the parietal-temporal cortex. Patients are also told to write spontaneous sentences and copy pentagon images, all of these to assess executive functions.

Previous studies have shown that CKD patients have increased the risk of cognitive impairment; a study by Patel (2015) showed 70% of hemodialysis patients have moderate to severe cognitive impairment and is independently related to hemodialysis.[4,5,6,7,8]A study by Imelda et al (2015) showed a negative correlation between dialysis vintage and cognitive function.[24]However, a study by Siska et al (2015) showed the initiation of renal replacement therapy (RRT) increase the subjects' mean MMSE score from 27.6 to 28.5.[25] A study by Oghenekaroet al (2012) with 190 subjects also showed increased MMSE score in subjects after initiation of hemodialysis.[26] These evidence suggest that although end-stage renal disease (ESRD) and its comorbidities and complications are risk factors for cognitive impairment, renal replacement therapy contributes to its prevention and reduction. This is further supported with a study by Senda et al (2014) that showed a decreased level of MG after hemodialysis.[27]In our study, the subjects' mean MMSE score is above the cutoff point for cognitive impairment. However, over one-third of the subjects have cognitive impairment (score < 25), with the lowest score only 22 (mild impairment).

In this study, a negative correlation between MG level and MMSE score was found. This result is consistent with currently available evidence, such as a study by Angeloni et al (2014) in 267 patients aged 75 or older that showed increased MG level is associated with accelerated cognitive function decline.[28]Another study also showed an increase of 1 µmol/L of MG is associated with a 0.36 decrease in MMSE score.[15]The negative correlation found in this study shows that even mild cognitive impairment in patients aged 40-60 years old is statistically correlated with increased MG.

Multiple strategies can be implemented to reduce the levels of AGE products in CKD patients such as MG. Since MG is a protein-bound uremic toxin, therefore having low free-fractions in the blood causing ineffective removal by regular dialysis. Therefore, the removal of toxin can be increased by using a high-flux membrane, adding convection by ultrafiltration, and adjustments of extracorporeal treatments such as using dialyzer membranes with large pores and/or high adsorptive dialyzer.

This study has several limitations, such as the inability to exclude "silent stroke" with CT-scan. This study also cannot analyze confounding factors for cognitive impairment such as blood pressure and diabetes due to the limited number of subjects. Future research should include analysis of confounding factors, relationships between MG and MMSE score changes, and dialysis adequacy.[29]

CONCLUSION

Increased MG level is correlated with cognitive function impairment. This finding may explain the role of methylglyoxal on the pathogenesis of cognitive function impairment in hemodialysis patients. This finding can also be used for further improvement in patient care, with the cognitive function being considered as hemodialysis adequacy parameters.

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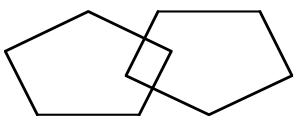
Appendix

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Appendix

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Source:

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