[*Putra * et al., 6(7): July, 2019*]

ISSN: 234-5197
Impact Factor: 3.765

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

THE CORRELATION BETWEEN SEVERITY OF DIABETIC NEUROPATIC WITH COGNITIVE FUNCTION DISORDERS IN PATIENTS DM

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DOI: 10.5281/zenodo.3517849

Keywords: Cognitive function, diabetic neuropathy.

Abstract

Background: Diabetic neuropathy and impaired cognitive function are complications that often occur in patients with diabetes mellitus (DM). both of these complication have pathophysiology mechanism which is almost the same. This study was to determine the correlation between the severity of diabetic neuropathy and impaired cognitive function in DM patients.

Methods: This study used a cross-sectional design in patients with diabetic neuropathy in the Endocrine Polyclinic and Neurology Polyclinic at Haji Adam Malik Hospital Medan, assessment of diabetic neuropathy was performed by anamnesa , neurological examination and nerve conduction velocity (NCV) and categorized as mild, moderate, severe. Furthermore, a cognitive function examination was performed using Montreal Cognitive Assessment - INA (MoCA-INA) ,Verbal fluency test , Trail Making Test A (TMT-A) and Trail Making Test B (TMT-B) . To analyze the correlation between the severity of diabetic neuropathy and cognitive function, fisher exact test was used.

Results: This study involved 31 patient subjects DM who suffer from diabetic neuropathy with The history of suffering DM had a median value of 4 (1-15) years, HbA1c of subjects had a median value of 8 (7-11.20). From the statistical analysis, it was found that there was a significant correlation between the severity of diabetic neuropathy with the four cognitive examination tools , MoCA INA with $p < 0.001$, TMT-A with $p < 0.023$, TMT-B with $p < 0.38$ and VFT with $p < 0.014$.

Conclusion: There is a significant correlation between the severity of diabetic neuropathy and impaired cognitive function in DM patients.

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases with characteristics of hyperglycemia that occur due to abnormal insulin secretion, insulin action or both. The *World Health Organization* (WHO) predicts an increase in the number of people with DM which is one of the global health threats . [1]

Patients with uncontrolled DM usually experience complications, especially microvascular conditions, including diabetic neuropathy characterized by progressive nerve damage, which leads to different clinical presentations, including Diabetic Neuropathy. [2] The incidence of diabetic neuropathy in diabetics is quite high, as shown through research conducted at the Mayo Clinic, where 47% of diabetics have neuropathy. Other studies report the prevalence of diabetic neuropathy reaching 70% in patients who have type two diabetes for 25 years or more. [3.4] There are two main mechanisms that are thought to have an important role in the occurrence of diabetic neuropathy, namely vascular disorders and metabolic disorders. [6]

Examination using the scoring method continues to develop, but still has limitations in establishing neuropathy as early as possible. NCV is the most sensitive and specific examination in detecting the incidence of diabetic neuropathy. NCV inspection is recommended to confirm the diabetic neuropathy is quantitative in clinical practice. [5]

In the past few years, impaired cognitive function has also been proven as a complication of DM. Although pathogenesis has been associated primarily with insulin signaling disorders, several studies have shown that it

can also occur through several pathogenesis pathways such as oxidative stress, inflammation , dyslipidemia, and others . [2]

There are several possible causes that explain the correlation between DM and decreased cognitive function. DM has been known as a risk factor for cerebrovascular disease that is also associated with hypertension and dyslipidemia, so that cognitive changes that occur may be mediated by cerebrovascular disease. This may appear more clearly in older age groups. Yaffe et al. (2012) state that the condition of hyperglycemia contributes to impaired cognitive function through several mechanisms such as the formation of advanced glycation end products (AGE), inflammation, and microvascular disease. Hyperglycemia can also increase the production of sorbitol which will damage blood vessels and cause nerve cell degeneration which will result in dementia and impaired cognitive function. [9]

There are several reports about the correlation between peripheral neuropathy and cognitive impairment. However, interestingly, it has been reported that the development of diabetic nephropathy, retinopathy depends on the severity of diabetic neuropathy. Therefore, it is possible that diabetic neuropathy is also associated with cognitive decline. In any case, further prospective studies regarding this association will be needed. [10]

In a study conducted by Moreira et al. In 2015, they assessed the correlation between impaired cognitive function and the severity of diabetic neuropathy. The results of the study showed that there were no differences found between patients with and without diabetic neuropathy in all cognitive tests (p> 0.05 in all comparisons). There is no found k between the relations *NSS, NDS* and one cognitive test. This study are advised to compare the NCV with an impaired cognitive function to get more accurate results. [2]

Method

Study sample
The research subjects were taken from H Hospital patient population. A and Malik in Medan. Determination of research subjects was carried out according to consecutive non random sampling method and there were 31 patients with diabetes mellitus who has diabetic neuropathy that meets the inclusion criteria and willing to give approval by signing an informed consent so included in the study.

Design study
This research is descriptive analytical with a cross sectional data collection method without treatment in the primary data source. The severity of diabetic neuropathy in this study was determined using an alternative approach proposed by tesfaye (2010). Stage 0 : no signs and symptoms and normal NCV examination, Stage 1: asymptomatic neuropathy, where there are no signs and symptoms but NCV and abnormal neurological examination in this study are defined as mild neuropathy, stage 2: symptomatic neuropathy, where there are signs and symptoms accompanied by abnormal NCV examination in this study was defined as moderate neuropathy, stage 3: severe polyneuropathy. In this study it was defined as severe neuropathy. To assess cognitive function performed using MoCA-INA, Verbal fluency test , TMT-A and TMT-B.

Statistic analysis
Research data is statistically analyzed with the help of a *Windows* computer program *SPSS (Statistical Product and Science Service)* version 22.0and to analyze the severity of diabetic neuropathy with cognitive function in patients with diabetes mellitus using *Fisher's Exact* test.

Results
All patients with diabetes mellitus are undergoing treatment at the Clinic of Endocrinology and Neurology Clinic Haji Adam Malik Hospital in Medan on the month December 2018 to febuary 2019, there are 31 patients with diabetes mellitus who experience diabetic neuropathy participated in the study.

Based on the characteristics of 31 research subjects, the age of all study subjects had a median of 54 (50 - 73) years. Research subjects with female sex were 26 subjects (83, 9 %) and men as many as 5 subjects (16.1%). The education level of the research subjects was divided into 5 groups where the Diploma was 17 subjects (54 , 8 %), High school as many as 8 subjects (25.8%), Bachelor Degree 4 Subjects (12.9%), Elementary school as many as 1 subject (3.2%) and Junior high school as much as 1 subject (3.2%). Long history of suffering from DM all study subjects had a median of 4 (1- 1 5) year , divided into <5 years as many as 16 subjects (51.6%), 5 - 10 years as many as 12 subjects (38.7%), and> 10 years as many as 3 subjects (9.7%). Hba1c levels in all study subjects had a median of 8 (7-11.20). For complete data on the characteristics of the subject of this research are presented in table 1.

Table 1. Overview of Characteristics of Research Subjects

Characteristics of respondents	Median	n (31)	Percentage (%)
Age	54 (50-73)		
Gender			
• Man		5	16,1
• Women		26	83.9
Education			
• Elementary school		1	3.2
• Junior high school		1	3.2
• High school		8	25.8
• Diploma		17	54.8
• Bachelor		4	12.9
History of DM (year)	4 (1-5)		
• <5 years		16	51.6
• 5 - 10 years		12	38.7
• > 10 years		3	9.7
Hba1c level (%)	8 (7-11.20)		

Based on the characteristics of the severity of diabetic neuropathy, MoCA -*INA*, TMT-A, TMT-B and *Verbal fluency test* in 31 research subjects In this study, there were 23 subjects (74.2%) with mild diabetic neuropathy, 8 subjects (25.8%) with moderate diabetic neuropathy and no subjects with severe neuropathy were found. MoCA - INA overall has a mean of 23.00 ± 2.84, there are 20 subjects (64.5%) with normal MoCA - INA values and 11 subjects (35.5%) *with* abnormal MoCA-INA values.

In this study there were 16 (51.6%) subjects with normal TMT-A values and 15 subjects (48.4%) with abnormal TMT-A scores. 17 subjects (54.8%) with normal TMT-B and 14 subjects (45.2%) with TMT-B abnormal. In this study it is said to be abnormal if there is an error and / or completion time for TMT-A more than 180 seconds and for TMT-B more than 300 seconds. 16 subjects (51 , 6 %) with abnormal *Verbal Test* scores and 15 subjects (48.4%) with *Verbal fluency test* normal. This can be seen in table 2 below.

Table 2 . Characteristics of severity of diabetic neuropathy, MoCA score -INA , TMT-A, TMT-B and Verbal fluency test (VFT)

Score Characteristics	Average	n (31)	Percentage (%)
Degree of diabetic neuropathy			
• Light		8	25.8
• Is being		23	74.2
• Weight		0	
MoCA-INA score	23.00 ± 2.84		
		11	35.5

• Normal (> 26)	20	64.5
• Abnormal (<26)		
TMT-A score, time		
• <180 seconds	16	51.6
• ≥ 180 seconds	6	19.4
• Not completed	9	29.0
TMT-A score, error		
• Not	16	51.6
• Yes		
- Time <180 seconds	6	19.4
- Time ≥ 180 seconds	9	29.0
TMT-B score, time		
• <300 seconds	17	54.8
• ≥ 300 seconds	7	22.6
• Not completed	7	22.6
TMT-B score, error		
• Not	17	54.8
• Yes		
- Time of <300 seconds	7	22.6
- Time ≥ 300 seconds	7	22.6
Verbal Fluency Test Score		
• Normal (≥ 18 names)	15	48.4
• Abnormal (<18 names)	16	51.6

In this study, based on *Fisher's Exact* test statistical analysis of the 31 subjects, showed that there is a significant correlation between the severity of diabetic neuropathy kat ting dysfunction cognitive, where *tools* to assess cognitive function using MoCA-INA with a *p* value of <0.001 TMT-A with a *value of p* <0.023 TMT-B with *p* <0.38 and VFT with *p* <0.014. Hi, this can be seen in the table below.

Table 3 . The correlation between the severity of diabetic neuropathy and the score Montreal Cognitive Assessment - INA

	Montreal Cognitive Assessment - INA		
severity of diabetic neuropathy	Normal	A normal	*P*
mild	7	1	0.001
moderate	4	19	

test *Fisher's Exact*

Table 4 . The correlation between the severity of diabetic neuropathy and the score Trail Making Test A (TMT-A)

	Trail Making Test A		
severity of diabetic neuropathy	Normal	A normal	*p*
mild	7	1	0.023
moderate	9	14	

test *Fisher's Exact*

Table 5 . The correlation between the severity of diabetic neuropathy and the score Trail Making Test B (TMT-B)

	Trail Making Test B		
severity of diabetic neuropathy	Normal	A normal	*p*
mild	7	1	0.038
moderate	10	13	

test *Fisher's Exact*

Table 6 . The correlation between the severity of diabetic neuropathy and the score Verbal fluency test (VF T)

	Verbal fluency test		
severity of diabetic neuropathy	Normal	A normal	*p*
mild	7	1	0.014
moderate	8	15	

test *Fisher's Exact*

Discussion

The age characteristics of diabetic neuropathy patients are almost the same as in previous studies conducted by Hutapea et al (2016) which mention the age range that most suffered from neuropathy was at the age of 45-65 years . [12] Other relevant research also states that the age range of suffering from diabetic neuropathy is most commonly experienced in the 51 - 59 year age range of 52.7 %. [13]

The number of patients with neuropathy in the age range of 45-65 years is caused by old age related to the accumulation of free radical damage such as increased levels of lipid peroxide and changes in enzyme activity which end with tissue damage in old age. [14]

In this study the most sex characteristics of diabetic neuropathy patients were 26 women (83,9 %). The results of this study are relevant to a previous study conducted by Rahmawati and Hargono (2018) where majority case group and the control group were female. [13] Other relevant studies suggest that the majority of diabetic neuropathies are experienced by women rather than men. [12]

In this study, the median long history of diabetes mellitus in patients with diabetic neuropathy for four (1-15) in 16 subjects (51.6%). The results of this study are relevant to previous studies by Hutapea et al (2016) that assessed the clinical picture of neuropathy in diabetic mellitus patients at the Neurology Polyclinic of RSUP Prof. Dr. RD Kandou most neuropathic patients were patients with long-standing diabetes in a range of 1-5 years, as many as 52 people from 83 subjects. [12] other study relevant states that diabetic peripheral neuropathy experienced by patients with diabetes have occurred since 3-5 years after a diagnosis of DM. [11]

Tamer et al. (2006) in Turkey that examines the prevalence and risk factors in 191 patients with DM neuropathy find significant association between long suffering from diabetes with diabetic neuropathy (OR = 1.010, CI 95% (from 1.004 to 1.015). The results of another study stated that the length of time a person experiencing DM along with complications that will be caused, meaning that the longer the experience of DM, the higher the incidence of complications experienced by patients.

Long suffering from DM has a close correlation neuropathy diabetic. Chronic hyperglycemia condition causes a decrease in insulin secretion or a decrease in the sensitivity of insulin. Excess glucose will enter the polyol pathway, so that glucose turns to sorbitol. Sorbitol formed will cause intracellular osmotic stress on nerve cells so that it can cause nerve cell damage. In reducing high intracellular glucose, the *aldose reductase* enzymereduces the amount of glucose that enters the polyol pathway , but this also causes a reduction in *gluthathione* which then increases the production of the *Advanced Glycation End Product* so that it will eventually cause oxidative stress on nerve cells. The longer a person has diabetes, this process will continue for longer and will continue to cause further damage to the cells, especially nerves. [15]

The median value of Hba1c in this study approached with a previous study done by Meijer (2003) which stated the average Hba1c level in DM patients with diabetic neuropathy of 8.7% ± 1.4. [16] Multicenter research conducted by the study group *The European Diabetes Prospective Complications Study* reports the progression of diabetic neuropathy is strongly associated with diabetes duration and levels of HbA1c.

In this study, based on *Fisher's Exact* test statistical analysis of the 31 subjects, showed that there is a significant correlation between the severity of diabetic neuropathy kat ting dysfunction cognitive. The results of this study are relevant to the research conducted Valkova et al (2011) that confirms that diabetics with polyneuropathy have a higher risk of experiencing a decrease in global cognition, impaired verbal short-term memory, the memory of which is delayed and retention of visual information, as well as the increased likelihood of mood depression . [17]

There is some reports regarding the correlation between peripheral neuropathy and cognitive impairment. However, interestingly, it has been reported that the development of diabetic nephropathy, retinopathy depends on the severity of diabetic neuropathy (Hotta et al., 2012) . Therefore, it is possible that diabetic neuropathy is also linked to cognitive decline. [10]

This study is not relevant to the study conducted by Moreira et al (2015), they assessed the correlation between cognitive impairment and the severity of diabetic neuropathy. For assessment of neuropathy using *Neuropathy Disability Score* (NDS) and *Neuropathy Symptom Score* (NSS) used. Global cognitive function was assessed using the *Mini mental state examination* (MMSE), *T rail making test A and B* and *Verbal Fluency Test* .The results of the study showed that no difference was found between patients with and without diabetic neuropathy in all cognitive tests (p> 0.05 in all comparisons). There was no correlation between NSS, NDS and any of the cognitive tests. [2]

Diabetic neuropathy and impaired cognitive function have almost the same pathophysiological pathways where pathophysiologist from both can occur due to metabolic disorders, including increased glycolysis processes that can cause excess mitochondrial transport bonds and the formation of reactive oxygen species (ROS), aldol se track reductase or polyol line , increase lane advanced glycation end product (AGE), oxidative stress, activity of poly adenosine diphosphate (ADP) -ribose polymerase (PARP), activation of protein kinase C (PKC) , pathway enhancement hexosamine, activation of mitogen activated protein kinase (MAPK) and inflammation the damage due process.

Limitations on this study is focused on assessing the correlation between the severity of neuropathy and cognitive function in subjects who have been diagnosed with diabetes mellitus with diabetic neuropathy without assessing more in other variables to give a representative result, where theory and many previous studies have men explain that diabetic neuropathy and disorders Cognitive function is part of the complications that often occur in DM patients and there are other variables that can be very relevant for the correlation between diabetic neuropathy and impaired cognitive function such as *body mass index* , blood sugar control and lipid profile. Other variables were not accessed in this study.

Conclusion

There is a significant correlation between the severity of diabetic neuropathy and impaired cognitive function in DM patients.

Suggestion

Consideration of cognitive function screening in DM patients with diabetic neuropathy, and vice versa screening for diabetic neuropathy in DM patients with impaired cognitive function so that therapy and education of patients can be holistic and further research is needed on the severity of diabetic neuropathy with cognitive function by factors other comorbidities in DM patients.

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