Prevalence of Executive Dysfunction in Type 2 Diabetes Mellitus Patients in Mataram

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Indroduction

Diabetes is currently becoming a global health problem in both developed and developing countries. The global prevalence of this disease in 2014 was 8.5% (WHO, 2016) and is estimated to increase to 10.4% in 2040 (Fan, 2017). The global prevalence of diabetes mellitus in Indonesia is still not determined yet, but a study conducted in Jakarta showed that its prevalence in productive age urban population is 4.6% (Mihardja, Soetrisno, & Soegondo, 2014). Type 2 diabetes mellitus is the most common type of diabetes mellitus, which is about 90% of all diabetes mellitus cases (Zheng, Ley, & Hu, 2018). Type 2 diabetes mellitus patients are at higher risk for developing cognitive impairment and dementia (Umegaki 2014).

Cognitive impairment is the main consequence of diabetes mellitus, particularly type 2 diabetes mellitus, which is currently getting a lot of attention from researchers in recent years. Since the prevalence of type 2 diabetes is becoming higher accompanied by its advanced treatment modalities, the life expectancy of the survivors is increasing. Hence, their risk of experiencing cognitive impairment as a result of diabetes mellitus-related neurodegenerative processes will also increase. Recently, the global prevalence of cognitive impairment related to diabetes mellitus is not available yet, but studies in various countries revealed that its prevalence is around 2.2% to 48.5% (Verny, Doucet, Bauduceau, Constans, Mondon, & Le Floch, 2015; Lavielle, et al., 2015; Damanik, et al., 2019). A study conducted in Indonesia showed a higher prevalence. It was related to high serum homocysteine levels, a well-known vascular risk factor for cognitive impairment (Damanik, et al., 2019). The wide range of prevalence of diabetes mellitus-associated cognitive impairment in various countries is influenced by many factors, including the demographic and clinical characteristics of the subjects studied and the study methods used (Kravitz, Schmeidler, & Beeri, 2013; Feinkohl, Price, Strachan, & Frier, 2015).

Type 2 diabetes mellitus-associated cognitive impairment may involve one or more cognitive domains, including attention, memory, language, visuospatial, and executive function (Mahmoud & Gawad, 2018). Executive dysfunction is known as one of the cognitive domains most affected by type 2 diabetes mellitus (Zilliox, Chandrasekaran, Kwan, & Russel, 2016). Individuals with type 2 diabetes mellitus-associated executive dysfunction have difficulty in planning, flexible thinking, and decision making that lead to a decrease in their quality of life and higher dependency on their caregivers (Rucker, McDowd, & Kluding, 2012). A serial process of neuroinflammation, oxidative stress, and glutamate excitotoxicity induced by insulin resistance-associated chronic hyperglycemia. It takes place in the frontal lobe and responsible for the occurrence of executive dysfunction in patients with type 2 diabetes mellitus (Moran, et al., 2013; Kim, 2019). Currently, the prevalence of executive dysfunction associated with diabetes mellitus is remain scarce.

However, early detection of type 2 diabetes mellitus-associated executive dysfunc- tion is beneficial for the patients since it will allow them, to get appropriate

treatment. Early diagnosis followed by optimal treatment of type-2 diabetes mellitus-associated executive dysfunction is effective to hamper its progres- sion to a more severe form of cognitive impairment so that they can carry out their daily functional and social activities properly (Sun, et al., 2020). By maintaining proper glycemic control, patients with type 2 diabetes mellitus-associated cognitive impairment, including executive dysfunction have better clinical outcomes compared to those with poor glycemic control (Miranda-Felix, Valles- Ortiz, & Ortiz-Felix, 2016). This study aimed at investigating the prevalence of executive dysfunction and identifying its associated demographic and clinical characteristics.

Method

This was a case-control study. It both type 2 diabetes mellitus patients and healthy subjects in the outpatient setting of Siti Hajar Islamic Hospital Mataram, West Nusa Tenggara, from May to September 2020. The sample calculation formula for comparing the proportion of two unpaired samples according to Wang and Chow was used to determine the sample size of this study (Wang & Chow, 2007). Since the lowest prevalence of cognitive impairment in patients with type 2 diabetes mellitus (P2) was 2.2% (Lavielle, et al., 2015), the minimum sample size required for each group was 41 using the sample calculation formula mentioned above. However, the number of eligible subjects obtained for each group during the period of this study was 53. The inclusion criteria for the type 2 diabetes mellitus subjects group were: type 2 diabetes mellitus patients aged 40-65 years old, fully conscious, and those with minimum graduation of elementary school. The inclusion criteria for the healthy subjects group were subjects without prior history of diabetes mellitus, aged 18-65 years old, fully conscious, and those with minimum graduation of elementary school. The exclusion criteria for both groups were subjects with significant uncorrected visual and hearing loss, prior history of cognitive impairment, depression, and taking an antidepressant and antianxiety drugs. This study was approved by Komisi Etik Penelitian Kesehatan of Universitas Mataram with Register Number 63/UN18. F7/ETIK/2020. All subjects signed written informed consent before their participation.

Demographic and clinical characteristics collected from both groups were age, gender, years of education, Trail Making Test Part B (TMT-B) completion time, and status of executive function. Demographic and clinical characteristics as categorical variables were collected only from subjects with type 2 diabetes mellitus. They were age (40-54 years vs 55-65 years), gender, years of education (≤12 years vs>12 years), duration of diabetes mellitus (<5 years vs ≥5 years), treatments (oral antidiabetics, insulin, combination, and no treatment), smoking, hypertension, coronary artery disease, the status of body mass index (BMI) (normo weight vs overweight), and dyslipidemia. Normoweight was defined as BMI <25 kg/m2, while overweight as BMI ≥25 kg/m2 (Indrayana & Harahap, 2020). The status of executive function was assessed using the TMT-B instrument. In TMT-B, the subjects were asked to connect circles containing numbers or letters scattered randomly in a paper in alternate number and letter sequences and its completion

time was recorded. The completion time was then categorized into normal (≤180 seconds) and prolonged (>180 seconds). Subjects with normal completion time in TMT-B were considered to have a normal executive function, whereas those with prolonged completion time were considered to have executive dysfunction. This instrument had been validated and used in the previous study (Harahap, Indrayana, & Amalia, 2017).

Statistical analysis used to compare the demographic and clinical characteristics between type 2 diabetes mellitus and healthy subjects were independent t-test, Mann- Whitney U test, and chi-square test. Simple and multiple logistic regression tests were used to examine the association between the characteristics of the subjects and the status of executive function. The analysis was performed using IBM SPSS 22.0 and statistical significance was set at $p<0.05$.

Results and Discussion

The previous study had shown that type 2 diabetes mellitus was associated with the incident of cognitive impairment ranging from mild to moderate to dementia (Munshi, 2017). Pathophysiologically, chronic dysfunction of pancreatic β-cell and insulin resistance, the hallmark of type 2 diabetes mellitus, will result in the chronic hyperglycemia and the increase of advanced glycation end- products deposition in most of the body tissues, including the brain. In the brain, these conditions will eventually activate a series of pathologic processes, including self-sustaining neuroinflammation, oxidative stress, and glutamate excitotoxicity that lead to neuronal death and neurodegeneration (Kim, 2019). Chronic hyperglycemia-induced oxidative stress found in diabetes mellitus taking place in the population of neurons in brain tissue, especially in the hippocampus, also contributes to increased the production of amyloid-β (Aβ) oligomers and decreased the elimination of them from the neurons. In neurons, the increased production of Aβ oligomers will then provide positive feedback to conditions of oxidative stress, hyperphosphorylation of tau protein, and the formation of neurofibrillary tangles (NFTs), a condition which is characteristic of Alzheimer's disease (Zilliox, Chandrasekaran, Kwan, & Russel, 2016). In type 2 diabetes mellitus, deposition of Aβ oligomers as well as hyperphosphorylation of tau protein, occurred via activation of neuronal glycogen synthase kinase 3 (GSK3) signaling pathway (Seto, Yang, Kiat, Bensoussan, Kwan, & Chang, 2015). These mechanisms support the theory that diabetes mellitus-associated cognitive impairment, including type 2 diabetes mellitus, can have clinical progression towards Alzheimer's dementia. The neurodegenerative process taking place in the particular brain area that serves particular cognitive functions, including attention, memory, language, visuospatial, and executive function will result in dysfunction of these cognitive domains (Palta, Schneider, Biessels, Touradji, & Hill-Briggs, 2014). A study conducted in Cipto Mangunkusumo National General Hospital revealed that the prevalence of cognitive impairment among type 2 diabetes mellitus patients aged <60 years old was 48.5% (Damanik, et al., 2019). This prevalence was higher compared with other studies showing its prevalence ranging from 2.2% to 28.8% (Verny, Doucet, Bauduceau, Constans, Mondon, & Le Floch, 2015; Lavielle, et al., 2015).

Previous article reviews stated

that executive function was one of the cognitive domains most affected in type 2 diabetes mellitus (Moheet, Mangia, & Seaquist, 2015; Munshi, 2017). A meta-analysis aimed to obtain the effect size for the most frequently reported neuropsychological test within domains revealed that the instrument most commonly used for the evaluation of executive function was Trail Making Test Part B (TMT-B) (Palta, Schneider, Biessels, Touradji, & Hill-Briggs, 2014). The present study showed that the prevalence of executive dysfunction in type 2 diabetes mellitus patients is significantly higher (49.1%) compared to healthy subjects with comparable age, gender, and years of education. The mean completion time in TMT-B, an instrument used to evaluate an executive function, in this study also showed significantly higher in type 2 diabetes mellitus patients compared with healthy subjects (Table 1). The prevalence of executive dysfunction revealed in this study was in line with the results of the previous study (Damanik, et al., 2019). Since the brain area serving executive function is located in the prefrontal cortex, the high prevalence of executive dysfunction among type 2 diabetes mellitus patients shown in this study might indicate the occurrence of pathologic processes described above in this brain area. A study using voxel-based morphometry confirmed that type 2 diabetes mellitus was associated with gray matter loss in some brain areas of the patients, including frontal lobes, the brain area that involved executive function (Moran, et al., 2013).

Table 1. Demographic and Clinical Characteristics of Type 2 Diabetes Mellitus and Healthy Subjects

Variables	Mean ± SD, Unless Otherwise Stated		p-value
	Type 2 DM (n=53)	Healthy Subjects (n=53)	
Age in years	52.75±5.86	51.49±6.05	0.277[a]
Gender, n(%)			
Male	23 (45.1)	28 (54.9)	0.331[b]
Female	30 (54.5)	25 (45.5)	
Years of education	12.25±3.93	13.45±3.52	0.101[a]
TMT-B completion time in seconds	192.34±85.66	118.92±49.72	<0.001[c]*
Executive function, n(%)			
Normal	27 (50.9)	47 (88.7)	<0.001[b]*
Dysfunction	26 (49.1)	6 (11.3)	

[a]Independent t-test, [b]Chi-square test, [c]Mann-Whitney U test.
*Significant difference (p<0.05)
SD: standard deviation; DM: diabetes mellitus; TMT-B: Trail Making Test Part B

Since the executive function is referred to the ability of subjects in planning, problem- solving, flexible thinking, problem solving, and decision making, dysfunction of this cognitive domain will decrease their functional capacities that lead to loss of productivity and high daily living independence (Rabonivici, Stephens, & Possin, 2015). Type 2 diabetes mellitus is known as an important risk factor for executive dysfunction, either in relation or independent from the existence of demographic characteristics and other vascular risk factors (Rucker, McDowd, & Kluding, 2012). Common vascular risk factors other than diabetes mellitus most

commonly identified are cigarette smoking, hypertension, coronary artery disease, overweight,and dyslipidemia (Rosjidi, Isro'in, & Wahyuni, 2017). These vascular risk factors modified the role of diabetes mellitus in the development of cognitive impairment (Kim, 2019). A cohort study also showed that increasing age, good educational level, and female gender were identified demographic factors that increased the risk of diabetes mellitus-associated cognitive impairment, including executive dysfunction (Ganguli, et al., 2014). The present study showed that among demographic and clinical characteristics of patients with type 2 diabetes mellitus, the female gender is the only variable significantly associated with the prevalence of executive dysfunction (Table 2). This is in line with the result of the previous study described above (Ganguli, et al., 2014).

Table 2. Association between demographic and clinical characteristics and status of executive function in subjects with type 2 diabetes mellitus

Variables	Executive function		Crude OR (95%CI)[a]	p-value	Adjusted OR (95%CI)[b]	p-value
	Normal (n=27)	Dysfunction (n=26)				
Age, n(%)						
40-54 years	15 (55.6)	13 (50.0)	0.80 (0.27-2.36)	0.686	-	
55-65 years	12 (44.4)	13 (50.0)	Reference			
Gender, n(%)						
Male	16 (59.3)	7 (26.9)	0.25 (0.08-0.81)	0.020*	0.25 (0.07-0.88)	0.030**
Female	11 (40.7)	19 (73.1)	Reference		Reference	
Years of education, n(%)						
≤12 years	15 (55.6)	19 (73.1)	2.17 (0.69-6.87)	0.187*	1.24 (0.34-4.54)	0.744
>12 years	12 (44.4)	7 (26.9)	Reference		Reference	
Duration of DM, n(%)						
<5 years	12 (44.4)	6 (23.1)	0.38 (0.11-1.23)	0.105*	0.36 (0.10-1.30)	0.117
≥5 years	15 (55.6)	20 (76.9)	Reference		Reference	
Treatments, n(%)						
OAD	15 (55.6)	17 (65.5)	0.76 (0.11-5.15)	0.775	-	
Insulin	5 (18.5)	5 (19.2)				
Combination	5 (18.5)	1 (3.8)				
No treatment	2 (7.4)	3 (11.5)	Reference			
Smoking, n(%)						
Yes	6 (22.2)	4 (15.4)	0.64 (0.16-2.58)	0.527	-	
No	21 (77.8)	22 (84.6)	Reference			
Hypertension, n(%)						
Yes	20 (74.1)	22 (84.6)	1.92 (0.49-7.57)	0.346	-	
No	7 (25.9)	4 (15.4)	Reference			
CAD, n(%)						
Yes	2 (7.4)	1 (3.8)	0.50 (0.04-5.87)	0.581	-	
No	25 (92.6)	25 (96.2)	Reference			
BMI, n(%)						
Normoweight	12 (44.4)	15 (57.7)	1.70 (0.58-5.06)	0.336	-	
Overweight	15 (55.6)	11 (42.3)	Reference			
Dyslipidemia, n(%)						
Yes	15 (55.6)	16 (61.5)	1.28 (0.43-3.83)	0.659	-	
No	12 (44.4)	10 (38.5)	Reference			

[a]Simple logistic regression, [b]Final model of multiple logistic regression
*Eligible for multiple logistic regression analysis (p>0.25), **Significant association (p<0.05)

The existence of other vascular risk factors as the comorbid of type 2 diabetes mellitus, including cigarette smoking, hypertension, dyslipidemia, and overweight contribute to aggravate the endothelial as well as blood-brain barrier dysfunction induced by chronic hyperglycemia-associated systemic inflammation and oxidative stress in patients with type 2 diabetes mellitus (Verma & Despa, 2019). Due to the blood-brain barrier dysfunction, the brain tissue becomes to be exposed to neurotoxic substances that are translocated from the circulating blood to the brain parenchyma, such as thrombin, fibrin, plasmin, hemoglobin, and iron derived from lysed erythrocyte cells (Biessels & Despa, 2018). Translocation of these neurotoxic substances into brain tissue will cause neuronal and glial cells dysfunction. It leads to neurodegenerative processes and cognitive dysfunction through various mechanisms previously described. A previous study examining the association between vascular risk factors mentioned above and the prevalence of executive dysfunction among type 2 diabetes mellitus patients showed many results. Kim reviewed the characteristics of cognitive impairment in patients with diabetes mellitus and showed that the common vascular risk factors mentioned above were associated with the development of cognitive impairment (Kim, 2019).

This review is supported by the results of a study conducted by Ganguli et al. showing these vascular risk factors were associated with the prevalence of cognitive impairment (Ganguli, et al., 2014). However, Xiu et al. investigated the risk factors for cognitive impairment among the older diabetes mellitus population and the results showed that smoking, hypertension, coronary heart disease, overweight, and dyslipidemia were not associated with the prevalence of diabetes mellitus-associated cognitive impairment (Xiu, Liao, Sun, & Chan, 2019). These results are following the results of the present study.

The level of education as an important component of cognitive reserve, in theory, determines the susceptibility of a patient with type 2 diabetes mellitus to suffer from cognitive impairment (Darwish, 2018). Cognitive reserve is the ability of the brain to use neuronal networks efficiently and flexibly in performing unique tasks in the presence of pathology in brain tissue (Stern, 2013). In this case, two subjects, who have relatively similar pathological conditions in the brain, may show different clinical outcomes, i.e. one subject shows intact cognitive function or obtain a significant improvement of cognitive impairment compared to others. Theoretically, a better level of education supports the ability of neurons in the brain to adapt to the existence of type 2 diabetes mellitus-induced pathological, so that they can function optimally. This means that those pathological conditions in brain tissue that lead to type 2 diabetes mellitus-associated neurodegenerative process, can be compensated for by the neuron population. In such a way that they can still carry out their daily functional activities properly. Theoretically, a better level of education induces neuronal activities reflecting the neuronal plasticity that existed in three forms. Namely neurogenesis, production of neurotrophic factors, and regulation of the neurotransmitter system (Vivar, Potter, & van Praag, 2013). However, following vascular risk factors, the present study showed that years of education were not associated with the prevalence of type 2 diabetes mellitus. Nevertheless, many results regarding the level of education, duration of disease, and vascular risk factors in both the previous and the present studies are mostly determined by the population of type 2 diabetes patients studied and the research method and instrument of cognitive assessment used.

This study has a limitation. The baseline data of executive function of the subjects before diabetes mellitus were not available. It is difficult

to determine whether the finding of executive dysfunction in this study is merely caused by diabetes mellitus or as a pre-existing condition. Therefore, the information about prior history of cognitive impairment, including executive dysfunction in this study was obtained from the information given by the patients and their relatives. However, due to the scarce data on the prevalence of executive dysfunction among patients with type 2 diabetes mellitus, the results of this study are becoming valuable for the local health authority to make policies regarding the detection and management of executive dysfunction among these patients. The findings of executive dysfunction in this study were not confirmed by brain imaging to identify the anatomical changes in the brain as described in the previous. However, for clinical practice, especially in rural areas, detection of executive dysfunction using simple neuropsychological testing provided in this study is sufficient for the basis of its management.

Conclusion

This study revealed a high prevalence of executive dysfunction among patients with type 2 diabetes mellitus. Gender was the only characteristics associated with the prevalence of executive dysfunction among these subjects. Being female is at higher risk of suffering from type 2 diabetes mellitus-associated executive dysfunction. Evaluation of the impact of executive dysfunction on the functional and social activities of daily living of patients with type 2 diabetes is recommended in future study.

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