Duration of Diabates Mellitus and Mild Cognitive Impairment among People with Type 2 Diabetes Mellitus in Semarang City, Indonesia

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Abstract. The prevalence of type 2 Diabetes Mellitus (T2DM) at Gunungpati Primary Healthcare Center (PHC) in 2017-2019 were 1,323, 1,168, and 864 per 100,000 population. Complications of DM are mild cognitive impairment (MCI), leg ulcers, and death. The prevalence of MCI among people with T2DM at Gunungpati PHC was 70% (54%-86%). We investigated the association of duration of T2DM and other risk factors with MCI. It was a case-control study. The sample was 68 cases and 68 controls. Variables were assessed with structured questionnaires and MMSE. Data were analyzed with logistic regression. Of the total 136 subjects, there were 61 subjects (44.85%) with duration of T2DM≥5 years and 75 subjects (55.14%) with duration of T2DM<5 years. After adjusted for other variables, risk factors associated with MCI were duration of T2DM (OR: 3.24; 95%CI: 1.42-7.42), age (OR: 6.67; 95%CI: 2.15-20.73), physical activity (OR: 3.65; 95%CI: 1.61-8.26), and stress (OR: 4.37; 95%CI: 1.36-14.06).

Keywords: Duration, T2DM, MCI

1 Introduction

Non-Communicable Diseases (NCD) cause more deaths than other causes, and it is projected that this number will continue to increase from 38 million deaths in 2012 to 52 million deaths in 2030 [1]. Seventy percent of the total deaths in the world and more than half the burden of the disease is Diabetes Mellitus (DM) [1]. Based on data from the Basic Health Research, the prevalence of people with DM aged 15 years and over increased from 6.9% in 2013 to 8.5% in 2018 [2]. In Central Java, the prevalence of DM was 20.6% after hypertension at 57.1% in 2018 [3]. While in Semarang City, DM cases increased signficantly after hypertension with the most cases in the age group of 45-65 years. In Gunungpati Primary Healthcare Center (PHC), the prevalence of Type 2 DM (T2DM) during 2017-2019 was 1,323, 1,168, and 864 per 100,000 population, respectively.

Some common complications of T2DM are Mild Cognitive Impairment (MCI), angina, dialysis, foot ulcers, proteinuria, amputations, peripheral arterial disease (PDA), heart disease and stroke, neuropathy (nerve damage), diabetic retinopathy, kidney failure, and death [4]. MCI is a condition of objective cognitive impairment based on neuropsychological tests with clinical symptoms leading to the occurrence of dementia [5]. The diagnosis of MCI is based on amnestic

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dysfunction, including learning, memory, perceptual, and central functions of executive impairment. Study showed that MCI is referred to as a clinical condition between aging and Alzheimer's disease in which a person experiences memory loss to a greater extent with age, but there are no clinical symptoms of Alzheimer's disease [6]–[10]

MCI is the prodromal stage of Alzheimer's disease which is influenced by gender differences. According to previous studies, T2DM is a risk of MCI that can develop into Alzheimer's due to vascular dysfunction, oxidative stress, and inflammation. Epidemiological studies show that T2DM is a risk factor for cognitive impairment, dementia, and Alzheimer's disease. Among people with T2DM, 41.6% of them did not have a cognitive impairment, 41.6% had MCI, and 16.8% had Alzheimer's disease [9]. The prevalence of MCI among people with T2DM at Gunungpati PHC was 70% (54%-86%).

The incidence of MCI is higher in individuals with T2DM than those who do not have T2DM. Although the pathophysiology of MCI in T2DM is unclear, many studies show that changes in pathoglycaemia, DM complications, and psychological status are significant risk factors. Previous research indicates that DM correlates with cognitive impairment and neurodegenerative diseases. Prevention on modifying the risk factors might reduce the risk of MCI and dementia [8], [9], [11]–[17].

Several studies of risk factors for MCI among T2DM patients have shown inconsistent results. It might be due to differences in study design, study subjects, diagnostic criteria for T2DM or MCI. However, it might also be due to the duration or severity of T2DM. In this case-control study, we investigated the association between duration of T2DM and risk factors of severity (such as age, sex, physical activity, BMI, hypertension, stroke, medication compliance, smoking, and stress) with MCI.

2 Methods

We did a case-control study with 68 cases and 68 controls. Case was defined as all subjects with T2DM who participated in this study and were found to be affected by MCI. Control was defined as all subjects with T2DM who participated in this study and were found to be cognitively normal. We assessed MCI among people with T2DM and the risk factors. i.e duration of T2DM, age, sex, physical activity, BMI, hypertension, stroke, medication compliance, smoking, and stress. MCI was assessed using Mini-Mental State Examination (MMSE), whereas the risk factors were assessed using structured questionnaire. We used logistic regression models to know the association between duration of T2DM with MCI after adjusted with other risk factors.

3 Results and Discussion

We assessed 136 subjects with T2DM. Based on demographic characteristics and risk factors (Table 1), there were 61 subjects (44.85%) with duration of T2DM $\geq$ 5 years and 75 subjects (55.14%) with duration of T2DM < 5 years. It also showed that 104 subjects aged 50-60 years (76.47%) and 32 subjects aged 40-49 years (23.52%). Then, there were 108 females (79.41%) and 28 males (20.58%). Subjects with risky physical activity were 73 (53.67%) and non-risky physical activities were 63 (46.32%). Then it is known that subjects with obese BMI were 39 (28.67%) and subjects with normal BMI were 97 (71.32%). Subjects who hypertension were 80 (58.82%) and subjects who did not have hypertension were 56 (41.17%). Subjects with

stroke were 14 (10.29%) and 122 subjects without stroke (89.70%). Then, there were 68 subjects (50%) who complied with taking the medicine and 68 subjects (50%) did not comply. Subjects who had smoking habits were 21 (15.44%) and did not have smoking habits were 115 (84.55%). Then, for subjects who had stress were 25 (18.38%) while those who were not stressed were 111 (81.61%).

Table 1. Demographic characteristic and risk factors among 136 people with T2DM in Semarang City, Indonesia

Risk Factors	N	%
Duration of T2DM		
≥5 years	61	44.85
<5 years	75	55.14
Age		
50-60 years	104	76.47
40-49 years	32	23.52
Sex		
Female	108	79.41
Male	28	20.58
Physical activity		
<3 times a week	73	53.67
≥3 times a week	63	46.32
BMI		
Obesity	39	28.67
Normal	97	71.32
Hypertension		
Yes	80	58.82
No	56	41.17
Stroke		
Yes	14	10.29
No	122	89.70
Medication compliance		
No	68	50.00
Yes	68	50.00
Smoking		
Yes	21	15.44
No	115	84.55
Stress		
Yes	25	18.38
No	111	81.61

The collected data were tested by chi-square test. It showed from Table 2 that some risk factors are associated with MCI (p value<0.05), i.e. duration of T2DM, age, physical activity, hypertension, medication compliance, and stress. Otherwise, sex, BMI, stroke, and smoking were not shown to be significantly associated with MCI. Based on the result from duration of T2DM, the Odds Ratio (OR) was 3.64 (95% CI: 1.79-7.43), which means that subjects who had duration of T2DM $\geq$ 5 years had a 3.64 times higher risk of getting MCI than those who had duration of T2DM < 5 years. In age variable, OR was 6.39 (95% CI: 2.42-16.87), which means that subjects aged 50-60 years had a 6.39 times higher risk of getting MCI than those who were 40-49 years. OR of physical activity, hypertension, medication compliance, and stress were 3.17

(95% CI: 1.57-6.41), 2.09 (95% CI: 1.04-4.19), 2.3 (95% CI: 1.16-4.58), and 3.14 (95% CI: 1.21-8.11), respectively. The risk of getting MCI among people with less physical activity, hypertension, lack of medication compliance, or stress was almost three times higher than in people with physical activity $\geq$ 3 times a week, no-hypertension, medication compliance, and no-stress.

Table 2. Bivariable analysis of risk factors of MCI among 136 people with T2DM in Semarang City, Indonesia

Risk Factors	Cases (n=68) n (%)	Controls (n=68) n (%)	OR (95% CI)	p-value*
Duration of T2DM				
≥5 years	41 (60.3)	20 (29.4)	3.64 (1.79-7.43)	0.01
<5 years	27 (39.7)	48 (70.6)		
Age				
50-60 years	62 (91.2)	41 (61.8)	6.39 (2.42-16.88)	0.01
40-49 years	6 (8.8)	26 (38.2)		
Sex				
Female	52 (76.5)	56 (82.4)	0.69 (0.3-1.61)	0.39
Male	16 (23.5)	12 (17.6)		
Physical activity				
<3 times a week	46 (67.6)	27 (39.7)	3.17 (1.57-6.41)	0.01
≥3 times a week	22 (32.4)	41 (60.3)		
BMI				
Obesity	17 (25.0)	22 (32.4)	0.69 (0.33-1.47)	0.34
Normal	51 (75.0)	46 (67.6)		
Hypertension				
Yes	46 (67.6)	34 (50.0)	2.09 (1.04-4.19)	0.04
No	22 (32.4)	34 (50.0)		
Stroke				
Yes	8 (11.8)	6 (8.8)	1.37 (0.45-4.2)	0.57
No	60 (88.2)	62 (91.2)		
Medication compliance				
No	41 (60.3)	27 (39.7)	2.3 (1.16-4.58)	0.02
Yes	27 (39.7)	41 (60.3)		
Smoking				
Yes	12 (17.6)	9 (13.2)	1.4 (0.55-3.59)	0.48
No	56 (82.4)	59 (86.8)		
Stress				
Yes	18 (26.5)	7 (10.3)	3.14 (1.21-8.11)	0.01
No	50 (73.5)	61 (89.7)		

*Chi-square test

The multivariabel analysis was done in the variables of duration of T2DM, age, physical activity, and stress. This model was the best model because all rik factors are significantly associated. It is adjusted for sex, BMI, hypertension, stroke, medication compliance, and smoking. The adjusted ORs were significantly elevated 3-fold for subjects with T2DM with duration of T2DM $\geq$ 5 years.

Table 3. Multivariable analysis of risk factors of MCI among 136 people with T2DM in Semarang City, Indonesia

Risk Factors	AdjOR (95% CI)*	p-value
Duration of T2DM	3.24 (1.42-7.42)	0.01
Age	6.67 (2.15-20.73)	0.01
Physical activity	3.65 (1.61-8.26)	0.01
Stress	4.37 (1.36-14.06)	0.01

*Adjusted for sex, BMI, hypertension, stroke, medication compliance, and smoking

The results showed that there was association between duration of T2DM and MCI. The duration of getting T2DM $\geq$ 5 years was associated with greater cerebral macrovascular disease, clinical cerebral infarction, and subclinical infarction that impaired cognitive function. Longer experience of T2DM is associated with chronic hyperglycemia, which increases the likelihood of microvascular disease and can contribute to neuronal damage, brain atrophy, and MCI [8]. Besides the duration of T2DM, the risk factors for age, physical activity, and stress also showed significant association to MCI. It is not only the elderly population who are likely to get MCI. Another study reported that the decline in cognitive function has started to occur in middle age, starting at 45-49 years of age. The risk of developing MCI in middle adulthood may increase if there are metabolic factors [7]. With increasing age, a degenerative process occurs in the brain which is characterized by brain atrophy. Atrophy in the hippocampus results in decreased memory function which causes MCI [18].

The study also indicated that the higher the physical activity, the better the cognitive function. The level of physical activity is positively related to brain volume, white matter volume, and gray matter volume. Physical activity can increase neurogenesis and neurotrophic factor brain derived neurotropic factor (BDNF) which can increase the resistance and growth of several types of neurons, including glutamanergic neurons. Brain derived neurotropic factor (BDNF) acts as a major mediator of synaptic efficacy, nerve cell liaison, and nerve cell plasticity. Significantly, this effect occurs in the hippocampus, the region of the brain where learning and memory are centered. Physical activity can increase brain vascularity and contribute to maintaining cognitive function during aging [17].

MCI is also determined by stress. The cells and tissues that are most susceptible to oxidative stress are brain cells. Oxidative stress can result in damage to glial cells and neurons which can lead to decreased cognitive function [19].

4 Conclusion

The study revealed that the duration of T2DM was significantly associated with MCI among people with T2DM. Based on multivariable analysis, we also know that not only duration of T2DM, but also age, physical activity, and stress also showed significant association to MCI.

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