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The impact of gender differences on the cognitive function of type 2 Diabetes Mellitus patients

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ABSTRACT

Introduction. Female sex is considered a risk factor for dementia. A limited number of studies have studied the role of gender differences on the cognitive function of type 2 diabetes mellitus (type 2 DM) patients with varying results. This study aims to determine the impact of gender differences on the cognitive impairment (CI) risk in type 2 DM patients.
Material and methods. This study used a case-control research design. Samples were recruited consecutively. Data were analyzed by Chi-square test and logistic regression, expressed in odds ratio (OR) (95% CI) with a significance level of P <0.05
Outcomes. Sixty patients with diabetes met the eligibility criteria. The bivariate analysis found that female gender [OR=3.75 (95% CI 1.23-11.38), P=0.017], low education level, and hypertension were associated with CI in type 2 DM. Independent risk factors for CI in type 2 DM from the multivariate analysis were low education level and hypertension.
Conclusions. Based on this study, female gender is not an independent risk factor for cognitive dysfunction in patients with type 2 DM.

Keywords: cognitive impairment, diabetes, gender, sex

INTRODUCTION

Impaired cognitive function is a common complication in patients with type 2 DM [1]. Various factors are strongly considered as being risk factors for CI in type 2 DM such as low educational level, poor glycemic control, and longer duration of type 2 DM [1–3]. The role of non-modifiable risk factors such as gender in CI has been studied and reported but still shows mixed results. Studies that specifically report the impact of gender differences on CI in type 2 DM are still limited, including in Indonesia.

Female gender is suggested as a risk factor for dementia [4]. The reasons for the increased risk of dementia in women are still unclear, but previous studies suggest that there are sex-specific etiological factors in addition to a relatively long-life span in women [5]. A limited number of studies have studied the role of gender differences in the CI of diabetic patients [6,7]. In a 2016 meta-analysis of 2.3 million diabetic patients, women have a greater risk of vascular dementia than men [6]. However, a Randomized Controlled Trial (RCT) Action for Health in Diabetes of intensive lifestyle intervention for 10 years in diabetic patients aged 45-76 years reported that women have a lower prevalence of mild cognitive impairment (MCI) by 30% and better cognitive performance than men [8].

On those bases, this study was conducted which aimed to prove the impact of gender differences as a risk factor for cognitive impairment in patients with type 2 DM.

MATERIAL AND METHODS

This study used a case-control design and was conducted at the diabetic center at Prof. Dr. I.G.N.G Ngoerah Hospital Denpasar in October-December 2022. The research sample was all type 2 DM pa-

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tients who met the eligibility criteria. The inclusion criteria were type 2 DM patients aged 45-65 years with (case group) or without cognitive impairment (control group) while the exclusion criteria were a history of stroke, depression, epilepsy, brain tumor, central nervous system infection, and severe visual and hearing impairment. The research subjects were taken by consecutive sampling.

The diagnosis of type 2 DM is established in all patients who have been diagnosed or undergone type 2 DM treatment by an internal medicine specialist at Prof. Dr. I.G.N.G Ngoerah Hospital based on HbA1c value ≥ 6.5% [9]. Examination of cognitive function using the Indonesian version of the Montreal Cognitive Assessment test (MoCA-Ina). Education level is divided into high (≥ 12 years) and low (<12 years) education categories. The exclusion of depression in the study subjects was carried out by examining the Hamilton Depression Rating Scale (HDRS) with a score limit of ≥ 8. Glycemic control was divided into good (HbA1c <7%) and poor (HbA1c ≥7%).

Bivariate analysis with the Chi-Square test was performed to assess the relationship between gender and CI. Other factors that may be associated with CI in type 2 DM such as glycemic control, hypertension, and education level were also examined in bivariate and multivariate analyses. All data were analyzed using the IBM Statistics SPSS version 25 program. The significance level was P <0.05, and the effect size was expressed in odds ratios (OR) with 95% confidence intervals (95% CI). The study protocol was approved by the Ethics Committee of Prof Dr. I.G.N.G Ngoerah Hospital.

OUTCOMES

The research subjects obtained were 30 people in each of the case and control groups with a total of 60 people. The baseline characteristics of the research subjects are presented in Table 1.

TABLE 1. Baseline Characteristics of Research Subjects

Variables	Case (n=30)	Control (n=30)
Age, mean ± SD (years)	55,10 ± 6,3	56,03 ± 5,6
Gender, n (%) Men Women	 14 (46,7%) 16 (53,3%)	 23 (76,7%) 7 (23,3%)
Education level, median (min-max) years	12 (0-20)	12 (4-18)
MoCA-Ina score, median (min-max)	22 (11-25)	27 (26-30)
HbA1c, median (min-max) %	7,25 (5,2-14)	6,6 (5,9-14)

Bivariate analysis between gender and other factors that can affect cognitive impairment in type 2 DM found that female gender, low education level, and the presence of hypertension were risk factors for cognitive impairment in type 2 DM (Table 2).

TABLE 2. Bivariate Analysis of Several Factors Associated With Cognitive Impairment in Type 2 DM

Variables	Case (n)	Control (n)	OR (95% CI)	P
Gender Women Men	 16 (53,3%) 14 (46,7%)	 7 (23,3%) 23 (76,7%)	 3,75 (1,23-11,38)	 0,017*
Education level Low High	 13 (43,3%) 17 (56,7%)	 4 (13,3%) 26 (86,7%)	 4,97 (1,38-17,81)	 0,010*
Glycemic control Poor Good	 17 (56,7%) 13 (43,3%)	 13 (43,3%) 17 (56,7%)	 1,71 (0,61-4,74)	 0,302
Hypertension Ya Tidak	 19 (63,3%) 11 (36,7%)	 10 (33,3%) 20 (66,7%)	 3,45 (1,19-9,99)	 0,020*

* P <0,05

The results of the multivariate analysis found that low education level and hypertension had a significant relationship with CI in type 2 DM or was independent risk factors for CI. Female gender was not found to have a significant relationship with CI in type 2 DM after multivariate analysis (Table 3).

TABLE 3. Multivariate Analysis with Logistic Regression

Variables	*Adjusted* OR	95% CI	P
Female gender	2,856	0,757-8,827	0,129
Low education level	4,151	1,017-16,938	0,047*
Hypertension	3,583	1,118-11,480	0,032*

* P<0,05

DISCUSSION

All research subjects were in the age range of 45-65 years. This was carried out to avoid confounding factors of old age over 65 years which is the peak incidence of CI in type 2 DM [10]. The case group had worse glycemic control based on HbA1c than the control group but these results were not significantly different based on the Mann-Whitney test (p=0.72). The results of the bivariate analysis of the four variables tested showed that female gender, low education level, and hypertension were significantly associated with CI in type 2 DM. Glycemic control was not significantly associated with CI in this study.

Results from previous studies still showed an inconsistent relationship between glycemic control and cognitive function in type 2 DM patients. Eugenia et al (2021) stated that poor glycemic control with HbA1c ≥7% increases the risk of cognitive impairment compared to the group with HbA1c <7 % [11]. Meanwhile, a cohort study concluded that hypergly-

cemia, as measured by HbA1c, had no predictive power on cognitive decline in 6-year follow-ups [12]. The results of our current study showed that patients with poor glycemic control reached half of all research subjects so this could affect the results related to glycemic control variables in this study. This could be due to the research location which was a central referral hospital with a high level of case severity.

Female gender is a risk factor for cognitive impairment in type 2 DM based on the results of bivariate analysis, however, based on the results of the multivariate analysis, gender is not an independent risk factor for this relationship. The CAROLINA-COGNITION study involving 3163 participants (38% women) with type 2 DM showed that women with type 2 DM have a higher risk of accelerated cognitive decline (ACD) than men. This is partly explained by the presence of depressive symptoms. After evaluation of vascular and diabetes-related risk factors, complications, and therapy, the main contributors to a higher risk of ACD in women remain unexplained [13]. The current study excluded the presence of depression in research subjects through the HDRS questionnaire so that it can be stated that there are factors other than depression that affect the relationship between female gender and cognitive function in type 2 DM sufferers.

A systematic study in 2016 stated that overall women with diabetes have a 19% greater risk of vascular dementia than men. Individuals with type 2 DM have a 60% greater risk of developing dementia than those without dementia, the additional risk being greater in women [6]. Contrary to some of those study results, a prospective cohort Study of Longevity in Diabetes (SOLID) found that women in late middle age have better cognitive performance than men in many cognitive domains and are independent of the presence of type 1 and type 2 DM [5].

The biological factors and mechanisms underlying different cognitive functions in women and men are still unclear. Sex hormones are known to be neuroprotective in both sexes and the results of several studies shed light on how a woman's hormonal profile can influence cognitive differences between genders. Women with estrogen deficiency show a decrease in verbal memory that is reversible with estrogen therapy or normal ovarian function [14].

Exposure to endogenous estradiol in women may play a greater risk of vascular dementia than in men. A study of post-menopausal women found that high levels of endogenous estradiol especially in women with diabetes carry a higher risk of dementia [15]. There was also evidence from autopsy studies that the higher risk of vascular dementia in women may be mediated by greater neurological microvascular damage in women [6].

Differences in the impact of diabetes on cerebral vasculature and brain structure may contribute to sex-specific differences. Thomas et al. in 2022 published research on the relationship between diabetes and brain structure, as well as diabetes and cognitive function according to gender-specific patterns. Multivariate analysis showed that diabetes was associated with an increased incidence of cerebral lacunar and atrophy in women but not in men. Diabetes is also associated with decreased cognitive function, processing speed, and language skills in women but not in men. In a study by Thomas et al, it was found that diabetes was not associated with an increased risk of brain structural abnormalities and cognitive performance in men. Additional adjustments for risk factors and cardiovascular disease did not change the effect estimate [16].

Age-mediated cardiovascular risks factors such as hypertension and heart disease may play a role in mediating the relationship between diabetes and structural brain abnormalities. However, a study by Thomas et al showed that the relationship was independent of age, lifestyle, cardiovascular risk factors, and cardiac disease [16]. Mechanisms that may influence susceptibility to vascular complications of diabetes include coagulation disorders, oxidative stress, endothelial dysfunction, and impaired vasodilatation [17]. Women with diabetes may experience a more pro-thrombotic state than men which can lead to brain lacunas and atrophy [18]. Women with diabetes also have higher levels of systemic inflammation and oxidative stress than men [16].

The degree of central adiposity in men and women with diabetes may also have significant value. There is evidence to suggest that women with diabetes have a worse cardiovascular profile than men, especially when central adiposity is measured [19]. This can be due to a longer period of development of diabetes in women. Women are more insulin-sensitive in middle age, and insulin sensitivity worsens more than men before a diagnosis of diabetes in women is reached. The longer duration before the formal diagnosis of diabetes may also lead to an increased incidence of other risk factors such as abdominal adiposity, and higher subclinical damage mediated by hyperglycemia [20].

Low education level and hypertension were found as independent risk factors for CI in type 2 DM from this current study. Low education has been consistently reported to be significantly associated with dementia from community studies of type 2 DM [21,22]. A higher education degree generally indicates a higher cognitive reserve and is associated with a lower risk of dementia. Low education is also associated with a lack of control over cardiovascular and cerebrovascular disease risk factors related

to behavioral aspects and the ability to access health services [23].

Hypertension is a major risk factor for cardiovascular and cerebrovascular disease. Hypertension is a risk factor for cerebral atrophy, cerebral small vessel disease, white matter damage, and stroke in middle age. Vascular dementia is associated with the development of white matter hyperintensity, micro-cerebral hemorrhage, and lacunar infarctions [24]. The results of our study are in line with research reported by Witari (2014) which states that hypertension is a risk factor for cognitive impairment in type 2 DM [25].

The factors that moderate the relationship between the female gender and cognitive impairment in type 2 DM patients cannot be concluded with certainty based on this study. Future research should include data related to women-specific risk factors such as complications of pregnancy and menopause, premature menopause, and a history of gestational diabetes. Further studies are needed to elucidate the associated mechanism between diabetes, brain structure, and cognitive function in women.

CONCLUSION

In our study, the female gender is not an independent risk factor for cognitive dysfunction in type 2 DM patients. Factors mediating the relationship between gender differences and cognitive function in type 2 DM patients need further research. Low educational level and hypertension are factors that significantly increase the risk of cognitive impairment in type 2 DM.

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