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Original Article

Evaluation of statins impacts on cognitive function among diabetic patients

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ABSTRACT

Aims:: The study was intended to evaluate the association of cognitive impairment with statins therapy among diabetic outpatients.
Methods: Mini-Addenbrooke's Cognitive Examination (M-ACE) was conducted for 280 cases in a cross-sectional study at Hospital Pulau Pinang. M-ACE score is 30, and the cut-off score for mild cognitive impairment is ≤ 21 and ≤ 16 for dementia.
Results: The cognitive impairment was distributed among 59 (55.1%) patients with mild cognitive impairment and 48 (44.9%) patients with dementia. From 177 patients using statins, about 80 (45.2%) cases had cognitive impairment. While from 103 statins non-users, only 27 (26.2%) had cognitive impairment. The relative risk of cognitive impairment associated with statins use in diabetic patients is (RR: 1.72, 95% CI: 1.2–2.48) and the excess relative risk is 72.4%. The absolute risk is 19%, and the number needed to harm is 6. Spearman's test indicated a positive association between statins usage and cognitive impairment incidence (r: 0.188, p-value: 0.002). However, Spearman's test showed a non-significant correlation amongst statins and dementia incidence (P-value: 0.587, RR: 1.16, 95% CI: 0.67–2.02).
Conclusions: Statins therapy has a higher association with cognitive impairment risk than statins-free treatment; however, there is no association between statin use and dementia incidence among diabetic patients.

1. Introduction

Cognition is the mental action or procedure of getting knowledge and understanding throughout, experience, senses, and thought. It encompasses processes such as attention, learning, memory, and working memory, problem-solving and decision-making, computation, comprehension, evaluation, judgment, reasoning, and production of language [1].

Cognitive impairment is when a person has a problem with concentrating, learning new things, remembering, or making decisions that may affect their daily life. Cognitive dysfunction ranges from mild to severe. With mild cognitive impairment (MCI), people may begin to notice changes in cognitive functions, but still, be able to do their everyday activities. Critical levels of cognitive decline can lead to losing the ability to understand the meaning or importance of something and capacity to talk or write, resulting in the inability to live independently [2].

Cognitive impairment is defined as an inclusive term to interpret any characteristic that operates as an obstacle to the cognition process [3]. The term may refer to discrepancies in global intellectual performance, as with mental defects. It may demonstrate specific deficits in learning disorders, or it may illustrate drug-induced cognitive/memory disability, such as that seen with benzodiazepines and alcohol [4]. It usually refers to a high characteristic, as opposed to the altered level of consciousness, which may be acute and reversible. Cognitive impairments may be caused by brain injuries, neurological disorders, or mental illness [5]. MCI has been proposed as a term for a confined area between healthy aging and dementia, especially Alzheimer's disease (AD) [6].

Prevalence evaluates of Mild assorted from 16% to 20% for most of the analyzed research. A few studies had a very high estimation

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that could be due to issues with non-participation or elements particular to the survey method [7]. Estimates from studies conducted in urban sites, multiethnic cohorts, and in clinic-based studies were also at the higher end of the spectrum [8]. Statins mainly are prescribed among elderly patients with many comorbidities and polypharmacy [9–21].

Moreover, the Mini-Addenbrooke's Cognitive Examination (M-ACE) is a novel assessment tool for cognition deficit developed in 2015 (Hsieh et al., 2015) [22]. Until the date of starting this study, M-ACE was not translated or adapted to Malay. Also, M-ACE was not applied to the Malaysian population to detect cognitive decline in diabetic patients under statin therapy. The current research was planned to evaluate the association of mild cognitive impairment (MCI) and dementia with statins therapy in diabetic dyslipidemia management (DDM).

1.1. Research question

Does statins therapy increase or decrease cognitive impairment and dementia among diabetic outpatients?

1.2. Significance of the study

Mild cognitive impairment (MCI) is a stage that is potentially amenable to interferences that may avoid more deterioration toward dementia; the stage of cognitive dysfunction that has a more massive effect on everyday behavior. The study may afford a more understanding of MCI and share to early detection of subjects with MCI. Patients with MCI may benefit from interventions that will decrease their risk of progression to dementia and may be eligible for treatment with disease-modifying drugs that reverse previous damage or prevent further decline when such therapy become available (Roberts & Knopman, 2013).

2. Materials and methods

2.1. Study population

A cross-sectional study involved 280 consenting patients were assessed using a pre-validated M-ACE at Pulau Pinang Hospital, Malaysia, in the period from February 2016 to March 2018. Patients with Alzheimer's disease, stroke, blindness, paralysis, parkinsonism, <40 years old, prescribed statins < 6 months, disability reading and writing were excluded. The study included 177 of statins users and 103 statins non-users diabetic patients.

2.2. Procedure and variable assessment

Mini-Addenbrooke's Cognitive Examination (M-ACE) measures the person' ability to attention, memory, language fluency and visuospatial. M-ACE score is 30, and the cut-off score for MCI is ≤ 21 and ≤ 16 for dementia (Hsieh et al., 2015) (used with permission). IBM SPSS 23.0 was used for data management. This analysis guided by the documentation strategy for "cross-sectional study designs and strengthening the reporting of observational studies in epidemiology (STROBE)" [23].

2.3. Statistical analysis

The data were managed using IBM SPSS V23.0. Categorical variables were demonstrated as a number and percentage. Parametric data were explained as the mean ± standard deviation. The normality of the variables was measured by the Kolmogorov-Smirnov test. Log transformation was performed on some of the skewed variables before analysis to reach a normal distribution [24]. Independent *t*-test and analysis of variance (ANOVA) estimated the differences amongst the means of continuous factors. While chi-square, Mann-Whitney U and Kruskal Wallis tests were used for evaluating the differences between the nominal and categorical variables. A confidence interval (95%) and P-value <0.05 were considered statistically significant. Mantel-Haenszel and analysis of covariance (ANCOVA) were used to monitor the influence of confounders. Ethical Consideration Spearman's tests and logistic regression were used to measure the strength and direction of the association between two variables [25].

2.4. Ethical approval

From the ethical viewpoint, this study tracked the processes of the registration in the Clinical Research Centre in Hospital Pulau Pinang and the registration in the National Medical Research Register (NMRR ID: NMRR-15-1068-25700) [26]. Every study phase was conducted under the supervision of experts and followed the tenets of the last update of the Declaration of Helsinki [27]. All contributors have signed an informed consent form. The confidentiality, dignity, and data of the subjects are safe and used for the research and publication purposes only.

3. RESULTS

M-ACE was conducted for 280 cases with a mean age (59.6 ± 11.1) years. The prescribed statins were 14.7% atorvastatin (20–80mg/daily), 4% lovastatin (20–60mg/daily), 2.3% rosuvastatin 20mg/daily and 79.1% simvastatin (10–40mg/daily). From 177 patients using statins, about 80 (45.2%) cases had cognitive impairment; with M-ACE score mean 21.4 (95% CI: 20.7–22.2). While from 103 statins non-users, only 27 (26.2%) had cognitive impairment, with M-ACE score mean 23 (95% CI: 21.8–24.1) as described in Table 1, Table 2 and Table 3.

The relative risk (RR) of cognitive impairment in diabetic patients that used statins is 1.72, (95% CI: 1.20–2.48) and the excess relative risk (ERR) is 72.4%. The absolute risk (AR) is 19%, and the number needed to harm (NNH) is 6, as described in Table 4 and Table 5.

Mann–Whitney *U* test indicated a significant statistical difference for the means of M-ACE scores between statins users and non-users' groups (*P*-value: 0.002). Chi-square showed a statistically significant difference in the incidence of mild cognitive impairment (MCI) among statins users and statins non-users' groups (*P*-value: 0.001), and Spearman's test indicated a positive association between statins usage and MCI incidence amongst diabetic patients (r: 0.188, *P*-value: 0.002). Binary logistic regression was significant (r^2: 0.036, p-value: 0.030). However, Spearman's test indicated a non-significant correlation amongst statins and dementia incidence (*P*-value: 0.587, RR: 1.16, 95% CI: 0.67–2.02).

4. Discussion

The relative risk (RR) of cognitive decline in diabetic patients that used statins is 1.73, and the excess relative risk (ERR) is 73%. The absolute risk (AR) is 19%, and the number needed to harm (NNH) is 6. Spearman's correlation test (*P*: 0.002), indicated a significant statistical difference for the mean of cognitive decline between statins users and non-users' cohorts.

Tukiainen et al., 2012 [28] found that mild cognitive impairment (MCI), was associated with decreases in both serum cholesterol and lipoprotein subclasses. Likewise, (Orth and Bellosta, 2012) have noted that cholesterol was vital to brain functions including learning and memory, although the contribution of cholesterol to these functions was complex [29]. Disruptions to sterol

Table 1
Demographic criteria distribution between cohorts with cognitive impairment and non-cognitive impairment among diabetic patients (n = 280).

Variance	No-Cognitive impairment (n = 173)	Cognitive impairment (n = 107)	P value
Age (years)	57.3 ± 10.1	63.4 ± 11.5	0.001
BMI (kg/m^2)	28.3 ± 4.8	28.5 ± 5.1	0.769
Gender			
Male	92 (53.2%)	76 (71%)	0.003
Female	81 (46.8%)	31 (29%)	0.003
Ethnicity			
Chinese	60 (34.7%)	41 (38.3%)	0.141
Indian	37 (21.4%)	43 (40.2%)	0.141
Malay	76 (43.9%)	23 (21.5%)	0.141
Alcohol	10 (5.8%)	18 (16.8%)	0.003
Smoking	47 (27.2%)	30 (28%)	0.874
Adherence			
Good	87 (50.3%)	50 (46.7%)	0.563
Poor	86 (49.7%)	57 (53.3%)	0.563
Patient activity	100 (57.8%)	59 (55.1%)	0.731
Income			
<1000	92 (53.2%)	60 (56.1%)	0.034
1000–1999	13 (7.5%)	29 (27.1%)	0.034
2000–4999	43 (24.9%)	15 (14%)	0.034
5000–10000	17 (9.8%)	3 (2.8%)	0.034
≥10000	8 (4.6%)	0 (0%)	0.034
Education level			
Primary	12 (6.9%)	13 (12.1%)	0.003
Secondary	91 (52.6%)	64 (59.8%)	0.003
Technical/Vocational	21 (12.1%)	19 (17.8%)	0.003
Bachelor	25 (14.5%)	9 (8.4%)	0.003
≥ Master	24 (13.9%)	2 (1.9%)	0.003
Education age	20.3 ± 6	18 ± 2.4	0.001
Living place			
Rural	35 (20.2%)	13 (12.1%)	0.082
Urban	138 (79.8%)	94 (87.9%)	0.082
Handedness			
Left hand	22 (12.7%)	3 (2.8%)	0.005
Right hand	151 (87.3%)	104 (97.2%)	0.005
Hypertension	130 (75.1%)	99 (92.5%)	0.001

BMI: Body mass index.
* *P* value < 0.05 was considered significant (2-tailed). Chi-square (X^2) test was carried out to detect the differences between the categorical variables. The *t*-test or Mann-Whitney *U* test, established on the skewness of data, were used for continuously distributed variables.

Table 2
Statin and HbA1c distribution between cohorts with cognitive impairment and non-cognitive impairment among diabetic patients (n = 280).

Variance	No-Cognitive impairment (n = 173)	Cognitive impairment (n = 107)	P value
Statin usage			
Non-statin usage	76 (43.9%)	27 (25.2%)	0.002
Statin usage	97 (56.1%)	80 (74.8%)	0.002
Dose intensity			
H-intensity statin dose	12 (12.4%)	14 (17.5%)	0.013
M-intensity statin dose	65 (67%)	52 (65%)	0.013
L-intensity statin dose	20 (20.6%)	14 (17.5%)	0.013
Type of statin			
Atorvastatin	11 (11.3%)	15 (18.8%)	0.098
Lovastatin	5 (5.2%)	2 (2.4%)	0.098
Rosuvastatin	3 (3.1%)	1 (1.25%)	0.098
Simvastatin	78 (80.4%)	62 (78.8%)	0.098
Diabetic status			
HbA1c%	8.1 ± 1.8	8.5 ± 1.9	0.042
Controlled HbA1c	70 (40.5%)	31 (29%)	0.052
Uncontrolled HbA1c	103 (59.5%)	76 (71%)	0.052
FBG (mmol/L)	8.1 ± 1.2	8.4 ± 3.5	0.828
FBG controlled	74 (42.8%)	43 (40.2%)	0.670
FBG uncontrolled	99 (57.2%)	64 (59.8%)	0.670
Diabetic period	14.1 ± 8.1	17.4 ± 10.8	0.004
Diabetes family history	85 (49.1%)	51 (47.7%)	0.208

HbA1c: Glycated hemoglobin, FBG: Fasting blood glucose.
* *P* value < 0.05 was considered significant (2-tailed). Chi-square (X^2) test was carried out to detect the differences between the categorical variables. The *t*-test or Mann-Whitney *U* test, established on the skewness of data, were used for continuously distributed variables.

homeostasis in the brain have been linked to MCI and Alzheimer's disease [30]. Cortes et al., 2013 found that brain cholesterol homeostasis was required for neural plasticity and memory functioning, and theorized that even subtle sterol metabolism deficits in the brain could contribute to memory, learning, and behavioral disorders in some individuals [31].

Table 3
Mini-Addenbrooke's Cognitive Examination scores amongst diabetic persons (mean ± SD) (n = 280).

Variance	No-Cognitive impairment (n = 173)	Cognitive impairment (n = 107)	P value
Attention	3.9 ± 0.3	3.7 ± 0.5	0.001
Memory	6.2 ± 0.9	3.9 ± 1.7	0.001
Fluency	5 ± 1.1	2.5 ± 1.4	0.001
Visuospatial	4.5 ± 0.6	3.4 ± 1.1	0.001
Memory recall	5.9 ± 1.1	2.9 ± 1.8	0.001
Total test score	25.4 ± 2.2	16.4 ± 4.2	0.002
Mild cognition impairment	0	59 (55.1%)	0.001
Dementia	0	48 (44.9%)	0.001
Re- test difference	0.046		
Equivalent test difference	0.044		
Cronbach's alpha	0.803		

* *P* value < 0.05 was considered significant (2-tailed). Chi-square (X^2) test was carried out to detect the differences between the categorical variables. The *t*-test or Mann-Whitney *U* test, established on the skewness of data, were used for continuously distributed variables.

Table 4
Contingency table of the effect of statins on mild cognitive impairment among diabetic patients.

Variable	Dementia	Mild Cognitive Impairment	Non-cognitive impairment	Total	Risk %
Statin user	31	49	97	177	0.452
Statins non-user	9	18	76	103	0.262
Total	40	67	173	280	0.382

Table 5
Descriptive of Mini-Addenbrooke's Cognitive Examination Scores among statin user and non-user.

	Statins			Statistic	Std. Error
Mini-Addenbrooke's Cognitive Examination Scores	Statin Non-user	Mean		22.981	0.5704
		95% Confidence Interval for Mean	Lower Bound	21.849	
			Upper Bound	24.112	
		5% Trimmed Mean		23.498	
		Median		24.000	
		Variance		33.509	
		Std. Deviation		5.7887	
		Minimum		7.0	
		Maximum		29.0	
		Range		22.0	
		Interquartile Range		7.0	
		Skewness		−1.268	0.238
		Kurtosis		.884	0.472
	Statin user	Mean		21.418	0.3805
		95% Confidence Interval for Mean	Lower Bound	20.667	
			Upper Bound	22.169	
		5% Trimmed Mean		21.726	
		Median		22.000	
		Variance		25.620	
		Std. Deviation		5.0616	
		Minimum		5.0	
		Maximum		29.0	
		Range		24.0	
		Interquartile Range		6.5	
		Skewness		−0.843	0.183
		Kurtosis		0.539	0.363

The pleiotropic effects of statins that in the long-term may affect cholesterol levels in the brain [32], although it has also been hypothesized that serum lipid metabolism changes may result in subclinical cognitive changes [28]. Several studies have identified these pleiotropic effects of statins as causal agents of cognitive change [33]. In their 2007 study, März et al., 2007 [34] found that statins produced a stellation in astrocytes, followed by rapid cell death. They cautioned that statins could be toxic to brain neurons and glial cells [35].

Kelley and Glasser, (2014) stated that cognitive data from several extensive epidemiological studies have not reliably demonstrated a robust association between incident cognitive decline and statin utilization, with some studies recording a protective effect, some indicating an increased risk and others finding no association. A small number of case series have described infrequent memory difficulties associated with statin use. In these series, the patients' cognitive signs resolute after statin stoppage. The existing medical literature does not propose that cognitive considerations should play a significant role in medical decision making to prescribe statins for diabetic patients. If a person is supposed to have idiosyncratic memory deficiency accompanying with the usage of statin medication, the drug can be discontinued [36].

A meta-analysis of 4 cohort trials (n > 4019) demonstrated a lower risk for mild cognitive impairment associated with statin use in patients with intact cognition at baseline (RR: 0.66; 95% CI: 0.51–0.86). On the other hand, systematic review (n = 20,536) revealed no difference in the incidence of cognitive impairment between statin and placebo use (RR, 0.98; 95% CI, 0.93 to 1.03) [37].

The review demonstrated no difference in Mini-Mental State Examination (MMSE) scores between placebo and statin use on global cognitive performance. With regards to declarative memory (n = 6434), processing speed (n = 6975), and visuoperception (n = 556), several RCTs demonstrated no difference between statins and placebo [38].

Suraweera, de Silva, and Hanwella (2016) stated that simvastatin is commonly prescribed for dyslipidemia to decrease CV hazard in patients. Some of these persons have dementia with the cognitive decline of numerous domains. Although protective properties seem to be present, there is emerging evidence that statins cause cognitive diminishing. The cholesterol role in cognitive function is complicated. The decrease in cholesterol levels seen with statins is effective in improving learning and memory in some patients. There is emerging proof that statins may deteriorate cognitive function. There are significant concerns over whether statins alleviate or aggravate cognitive complications. The association between cholesterol levels and cognitive function is still debated, mainly due to a shortage of robust evidence. They report the cases of two Asian patients who developed cognitive deficits after starting simvastatin. A 32-year-old man and a 54-year-old woman developed different but evident cognitive deficits that reversed after stopping simvastatin. The possibility of new-onset cognitive dysfunction and the decline of existing cognitive deficits should be considered when prescribing simvastatin to patients [39].

Following a review of potential side-effects, the UK Medicines & Healthcare products Regulatory Agency (MHRA) decided in 2009 that memory loss should be listed as a side-effect in the product information for all statins [40]. Similarly, in 2012, the US FDA required a statement to be added to the drug label for all statins that there was a potential for cognitive side-effects [41]. The basis for this decision was post-marketing event reports from individuals of ill-defined memory loss or decline that appeared to be reversible after stopping statin therapy, and not because there was high-quality evidence for a causal link. Indeed, a subsequent assessment of FDA surveillance databases found the reporting rates of cognition-associated adverse events for statins to be similar to those of other drugs used in patients with atherosclerotic disease [42].

A study by Smith et al. (2017) aimed to identify whether an association between statin usage and rate of cognitive impairment exists. The association between statins therapy and mild cognitive impairment (MCI) has been examined in the previous with the proof giving different outcomes. About seven hundred and sixty-eight persons were detected with mild cognitive impairment. Individuals were categorized into six probable cohorts depend on apolipoprotein E-ε4 allele prominence and utilization of statin therapy and evaluated for the deterioration in cognitive function. Wholly estimations of cognitive function leaning to less weakening with statin therapy, which support the situation that treatment with statins does not have an evident harmful influence on cognitive function and proposing a possible profit from statins therapy [43].

Statins block cholesterol, considered by many to be an important biochemical in the body, as it is mainly vital for cognitive function, and also block CoQ10 and dolichols [44], which are critical to mitochondrial function. There were almost 9,000 MedWatch documentations in the group of severe cognitive disorder: transient global amnesia (TGA) and memory loss. Note that confusion, disorientation, and forgetfulness which, most of the time are not reported to MedWatch or are considered mild. Statin-associated dementia can be diagnosed in case if the patient improves after stopping of the statin. The cognitive manifestations of statins may be just episodes of TGA. Growing of misperception, confusion, and amnesia or progressive dementia may resemble Alzheimer disease though differing in underlying pathology [45].

Glasser et al., (2010) assessed the association of statins use and type (lipophilic vs. hydrophilic) and cognitive decline. Cross-sectional analysis of 24 595 participants (7191 statin users and 17 404 nonusers) age ≥45 years, enrolled in January 2003 to October 2008. Cognitive damage was assessed with a tool of global cognitive status. Cognitive damage was considered as a score of <4. Overall, an association of cognitive injury and statin use was observed (8.6% of users' vs. 7.7% of non-users had cognitive decline, *P*: 0.014). However, after adjusting for variables known to be accompanying with cognition (age, CVD, education level, gender, income, race), the association was attenuated (OR: 0.98, CI: 0.87–1.10). No association was observed between statin type and cognition (OR: 1.03, CI: 0.86–1.24). Statin use and kind were slightly associated with dementia. After adjusting for variables that affect cognition, no association was observed [46], which tally with our findings.

Hydrophilic statins do not readily cross the blood-brain barrier (BBB), and lipophilic statins can enter the CNS more easily, are theorized to differ in their effects on cognition. CNS side effects of statins have been associated with their ability to cross the BBB. Statins ordered as (Most hydrophilic) pravastatin, rosuvastatin, fluvastatin, atorvastatin, lovastatin, and simvastatin (Most lipophilic) [47]. The idea of a various effect of statins based on their level of lipophilicity was supported by Ghodke et al., 2012 [48], who found that long-term therapy with simvastatin, but not with pravastatin, resulted in significant declines in brain cholesterol levels. One potential mechanism of action is through the relationship between cholesterol and myelin. Cholesterol is created through de novo processes in the brain. It is a rate-limiting in the development of myelin and contributes to the regulation of membrane fluidity and permeability. BBB protects the brain and nervous system from dietary sources of cholesterol. However, it is hypothetically possible that therapy with statins may reduce cholesterol synthesis in the brain, interfering with myelin formation. The highly lipophilic statins efficiently cross the BBB, while the hydrophilic statins are less likely to do so. According to a review of case studies, the majority, but not all, of the cases of statin-related cognitive decline have been associated with the more lipophilic statins [49].

Some argue that statins may even cause statin-induced dementia because fatty membranes cover axons and aid with cognitive activity. Statins, especially ones that cross the BBB, can harm axons by depressing the circulating levels of cholesterol and fatty acids, which provide insulation of axons [50].

5. Conclusion

The Malay version of the M-ACE is a brief, reliable and handy screening tool for the assessment of cognitive deficiency. Statins therapy has a higher association with cognitive impairment risk than statins-free treatment in outpatients with type 2 diabetes mellitus. Dementia progress is not related to statins therapy, but, the possibility of new-onset cognitive decline, the worsening of the existing cognitive deficit should be considered when prescribing a statin to diabetic patients.

Conflicts of interest

All authors have no inconsistency of interest to declare.

Authors' contributions

- MAH contributed in the conception of the work, data collection, data analysis, manuscript drafting, manuscript revising, and

approval of manuscript final, all aspects of the work and agreed for all aspects of the work.
- SASS contributed to the conception of the work, manuscript drafting, manuscript revising, and manuscript final approval and agreed for all aspects of the study.
- NAA contributed in the conception of the work, the manuscript drafting, manuscript revising, manuscript final approval and agreed for all aspects of the work
- DAMN contributed in the conception of the work, data analysis, manuscript drafting, manuscript revising, and approval of manuscript final and agreed for all aspects of the work.

The manuscript has been read and agreed by all the authors. The requirements for authorship as stated earlier in this document have been encountered. Each author deliberates that the manuscript represents honest work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.04.006.

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