Is metformin the only culprit for cognitive impairment in diabetes? [version 1; peer review: awaiting peer review]

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Abstract

Background: As patients with diabetes are conventionally on a long-term prescription for metformin, it is important to identify any increase in their risk for developing cognitive disorders due to metformin. Hence, an attempt was made to study the cognitive impairment by using Montreal Cognitive Assessment test (MoCA) as a possible predictor of development of cognitive impairment in type 2 diabetes patients on metformin therapy.

Methods: Four hundred type 2 diabetes patients on metformin were enrolled for this cross-sectional study, and data recorded. Cognitive test MoCA was administered and a score less than 26 was considered abnormal.

Results: In this study, the participants on metformin had a statistically significant correlation with age > 65 years, duration of diabetes (>5 years), metformin dose (1 gm and more) and presence of diabetes complications. Ordinal regressions showed significant correlation between abnormal MoCA scores and older age, longer duration of DM, and presence of one of the DM complications.

Conclusions: Amongst patients receiving medical therapy for control of type 2 diabetes, participants using metformin showed a very high prevalence rate of abnormal MoCA scores (85%). Increased duration of metformin intake leads to a decline in MoCA performance.

Keywords

Metformin, MoCA, diabetes mellitus, cognitive impairment.

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Introduction
Diabetes mellitus (DM) is a multifactorial disorder which leads to end-organ damage in many of the vital organs of the body, including the nervous system. Dementia and cognitive decline are increasingly being attributed to diabetes complications. Relationship between DM and cognitive decline is due to various diabetes-related factors (macro and micro-vascular complications, chronic inflammatory changes, persistent hyperinsulinemic state, resistance to the action of insulin, impaired metabolism of glucose or free radical mediated damage), cardiovascular related risk factors (elevated blood pressure, atherosclerotic coronary artery disease), and lifestyle related risk factors (dietary habits, smoking, lack of exercise).1–4

Treatment options for DM namely insulin and oral hypoglycaemic agents (OHAs) which can potentially prevent diabetes complications like cognitive decline and decrease the diabetes symptoms are of significant importance. Moreover, these treatment options may halt cognitive decline in diabetes patients through anti-inflammatory effects of the drugs or by targeting the vascular and neurodegenerative complications. Several studies have proven that better glycaemic control leads to improvement in several subjective and objective measures of cognitive performances.5–7

The frequently used OHA for treatment of diabetes is metformin. The mechanism of action of metformin is to prevent hepatic release of glucose, to improve peripheral utilization of glucose,8,9 to increase the sensitivity of insulin in the peripheral tissues and to restore signalling pathways of insulin.10 Metformin protects against neurodegeneration by decreasing insulin resistance, optimizing blood glucose levels, decreasing adiposity, and decreasing the production of atheromatous plaques. Apart from the peripheral actions, studies have shown that this drug also has neuroprotective properties on the nervous system and anti-inflammatory properties.9 An attempt was made here to study the cognitive impairment by using Montreal Cognitive Assessment test (MoCA)11 as a possible predictor of development of cognitive impairment in patients with type 2 diabetes on metformin therapy.

Methods
In this cross-sectional study, we enrolled 400 type 2 DM patients attending medical outpatient and inpatient departments of teaching hospitals attached to Kasturba Medical College, Mangalore. They were enrolled by consecutive patient selection, and if they satisfied the eligibility criteria demographic data and history were recorded, general physical examination and systemic examination were done and recorded. This study received ethics approval from Institutional Ethics Committee, Kasturba Medical College, Mangalore. The approval number is IEC KMC MLR 09-16/230.

All type 2 DM patients attending the outpatient and inpatient of teaching hospitals attached to Kasturba Medical College, Mangalore who satisfy inclusion criteria were enrolled in the study. Adults aged above 18 years of age with diabetes (ADA criteria) who were on metformin were included in the study. The patients were included only after obtaining written informed consent. Diagnosed cases of type 1 diabetes, thromboembolic disorders, mood disorder, depression, Alzheimer’s disease (AD) and other dementias were excluded.

The data collected included demographic details, detailed medical history, history regarding the present event, drugs used by the patients, physical examination findings and Montreal Cognitive Assessment (MoCA) test report.

Several factors responsible for decline of cognition which have also been associated with DM were included as covariates in this study. Variables noted like age, gender, educational qualifications, duration of DM, dosage and duration of metformin and other OHAs, and presence of DM complications.

For cognitive assessment Montreal Cognitive Assessment (MoCA) was used. MoCA is a screening tool for mild cognitive dysfunction. MoCA takes about 10 minutes to administer. It assesses the following domains of cognition: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Maximum possible score is 30 points. A score of >26 is considered normal. One point was added for an individual who has a formal education of twelve years or lesser, to give a possible maximum score of 30 points.

Statistical analysis for the study was conducted using the IBM SPSS Version 25.0 (RRID:SCR_016479). Subgroup analysis was done according to the dose and duration of metformin therapy, age and sex of the patient, presence or absence of other diabetes complications. The primary endpoint was presented as proportion of patients with cognitive impairment as detected on the MoCA. For the correlation between categorical variables chi-squared test or Fisher’s exact test was used. For the correlation between categorical variable with continuous variable an independent t test or Mann-Whitney U test was used. The variables that showed a significant association were further tested on an ordinal logistic regression. P value <0.05 was considered statistically significant.
Results
Table 1 describes characteristics of the study population. The oldest patient in our study was 83 years old and youngest was 34 years old. Majority of the participants in our study were between the age of 50 and 70 years. Our study population was predominantly male. The male to female ratio in the study was 2.1:1.

Most of patients included in our study had a duration of DM above 5 years (341), 59 patients who had DM for less than 5 years. Diabetic nephropathy was present in 34% of the subjects, while retinopathy and neuropathy were present in 12% and 39% of the subjects respectively.

Majority of our study patients were on metformin and sulfonylurea (SU) combination. Forty-two (10.5%) of the subjects were on insulin & metformin while 13.5% were on insulin, metformin & SU. Twenty-four (6%) were on metformin, SU & DPP4 inhibitors (DPP4I), 3.5% were on metformin, DPP4I & insulin, 8.3% were on metformin, SU, DPP4I & insulin, 2.3% were on metformin & thiazolidinedione, 6.3% were on metformin, SU & thiazolidinedione, 4.5% were on metformin & DPP4I, 2% were on metformin & alpha glucosidase inhibitors (AGI), 0.8% were on metformin, AGI & insulin, 0.5% were on metformin, thiazolidinedione & insulin.

Montreal Cognitive Assessment (MoCA) test was applied to all the subjects. A total MoCA score of twenty-six or more is considered normal.

In our study, 341 (85%) subjects had abnormal MoCA score i.e., less than 26 and only 15% had score more than or equal to 26. Scores below 26 and 17 indicate mild cognitive impairment (MCI) and dementia, respectively. In our study 124 patients had score below 17.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>57.3</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>2.1:1</td>
</tr>
<tr>
<td>Mean duration of diabetes</td>
<td>10.3 years</td>
</tr>
<tr>
<td>Diabetes complications</td>
<td></td>
</tr>
<tr>
<td>✓ Neuropathy</td>
<td>113/400</td>
</tr>
<tr>
<td>✓ Nephropathy</td>
<td>93/400</td>
</tr>
<tr>
<td>✓ Retinopathy</td>
<td>48/400</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>✓ Hypertension</td>
<td>231/400</td>
</tr>
<tr>
<td>✓ Dyslipidemia</td>
<td>287/400</td>
</tr>
<tr>
<td>✓ Smoking</td>
<td>166/400</td>
</tr>
<tr>
<td>✓ Alcohol consumption</td>
<td>154/400</td>
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<tr>
<td>✓ Pure vegans</td>
<td>57/400</td>
</tr>
<tr>
<td>Diabetes medications</td>
<td></td>
</tr>
<tr>
<td>✓ Metformin</td>
<td>400/400</td>
</tr>
<tr>
<td>✓ Sulfonylurea</td>
<td>213/400</td>
</tr>
<tr>
<td>✓ Thiazolidinediones</td>
<td>38/400</td>
</tr>
<tr>
<td>✓ DPP4 inhibitors</td>
<td>89/400</td>
</tr>
<tr>
<td>✓ Alpha glucosidase inhibitors</td>
<td>7/400</td>
</tr>
<tr>
<td>✓ Insulin</td>
<td>122/400</td>
</tr>
<tr>
<td>✓ Combination</td>
<td>84/400</td>
</tr>
<tr>
<td>MoCA*</td>
<td></td>
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<tr>
<td>✓ Abnormal</td>
<td>341</td>
</tr>
<tr>
<td>✓ Normal</td>
<td>59</td>
</tr>
</tbody>
</table>

* Dipeptidyl peptidase 4.
* Montreal Cognitive Assessment test.
Eighty-five percent of the subjects on metformin had abnormal MoCA scores, 91% of patients on SU drugs had abnormal MoCA scores while it was 78.5% in patients not on SU drugs. This correlation was very highly significant.

Ninety-five percent of patients on thiazolidinediones had abnormal MoCA scores while it was 84.5% in patients not on thiazolidinediones. This correlation was not statistically significant. While 98.9% of patients on DPP4I had abnormal MoCA scores it was 81.4% in patients not on DPP4I. This correlation was very highly significant. All patients on AGI had abnormal MoCA scores while it was 85% in patients not on AGI. This correlation was very highly significant. All patients on insulin had abnormal MoCA scores while it was 78.8% in patients not on insulin. This correlation was also very highly significant.

When we correlated MoCA with variables Table 2, we found statistically significant correlation with age >65 years, duration of diabetes (>5 years), metformin dose (1 g and more) and presence of complications. Running ordinal regression among the above significant variables we found the results depicted in Table 3 with significant correlation between abnormal MoCA scores and older age, longer duration of DM, and presence of one of the DM complications.

### Discussion

Since type 2 diabetes patients are conventionally on a long-term treatment with metformin, any association, if found between metformin use and cognitive impairment multiplies their risk for developing cognitive disorders. Such an association needs to be further evaluated and analysed as cognitive impairment. It is a diagnosable condition which can be monitored if detected early, and further deterioration can be halted.

The prevalence of abnormal MoCA scores of less than 26 (signifying cognitive impairment) was calculated to be 85% in the metformin users. This shows that those patients prescribed metformin for control of diabetes are at a higher risk for developing dementia. These results corroborate with the results of the case-control study carried out by Imfeld and colleagues in UK where amongst the metformin users, those who used 60 or more prescriptions of metformin showed a higher risk for developing AD with an adjusted odds ratio (AOR) = 1.71, 95% CI = 1.12–2.60, while those using anti-diabetic drugs did not show any altered risk for developing AD.
Our study did find a significant association between metformin use and an abnormal MoCA score of <26 (cognitive impairment) with a P-value of 0.006. The latest study done by Murray MD and colleagues was presented in International Alzheimer’s Association Conference. Of the study participants, 150 had used metformin. On follow-up, 87 participants developed dementia. After adjusting for age, gender, BMI, education, and APOE ε4 status, metformin use was associated with a greater risk for incident dementia (hazard ratio 2.28; P = .0152).

Limited evidence exists regarding the association between treatment options for DM and cognitive performance. The results of two longitudinal studies noted similar cognitive performance scores (TICS and a global score) for study participants without DM and for patients in the OHA treatment group. An Australian study showed that a greater decline in global cognition and executive functioning was observed in participants with diabetes. But, on analysing further, there was no relationship between the type of diabetic treatment (diet control versus OHA) and the fall in global cognitive performance. In contrast to this study, using Wechsler Logical Memory story recall Elias et al. showed poorer cognitive performance results among patients with DM, however on cognitive assessment using “immediate and delayed verbal memory on the story recall test” and “visual memory” the study group on insulin therapy performed more poorly compared to healthy controls. Notably, analysing the results of the seven neuropsychological tests, the performance of patients on OHA did not differ from the non-diabetic participant group. In the Primary Research in Memory (PRIME) study and the Australian Imaging, Biomarkers and Lifestyle (AIBL) study, Moore et al. studied the effects of DM and metformin use on cognitive performance. Among the study participants, metformin use was associated with worse cognitive performance (after adjusting for gender, age, depression, and educational qualification). However, only MMSE was used to measure cognitive function in this study. Also, this study did not analyse other treatments used along with metformin. This correlation was not significant after adjusting for B12 levels. In their study included a larger cohort wherein they assessed the effect of metformin on cognitive performance using MMSE. The results of the study (both cross-sectional and longitudinal analyses) showed significant protective effects of the drug metformin. In our study we did not asses vitamin B12 levels due to financial constraints. However, we found significant correlation with increasing age, dose and duration of metformin. Also, in our study we had 57 pure vegans and all of them had abnormal and low MoCA scores.

The ordinal regression data reveals a positive correlation between abnormal MoCA scores and older age, longer duration of DM, and presence of complications. Longer duration of DM can also signify longer duration of metformin usage. Metformin being the first line treatment, all the subjects in the study have been on metformin since they were diagnosed to have DM. Presence of complication and older age group as a positive correlation may signify that DM and aging are independent risk factors, as has been described in several studies.

There are a few limitations in this study. Firstly, lack of a control group without antidiabetic medications, the results of our study can only give preliminary conclusions, which needs to be further proved by larger multi-center clinical trials with higher sample size. The correlation between cognitive impairment in metformin users has been attributed to deficiency of vitamin B12, vitamin D and calcium. We did not assess these deficiencies in our study. Also, cognitive impairment is associated with stroke and other macrovascular diseases. In our study we did not analyse and correlate cognitive impairment with macrovascular complications. Many of our patients were on other anti-diabetic agents. The role of metformin alone causing cognitive decline cannot be ascribed. Also, the score we used for ascertaining cognitive decline, the Montreal Cognitive Assessment (MoCA), which has been earlier used in studies of dementia, but has not been used in diabetic population.

**Conclusion**

As per our study, the participants using metformin showed a very high prevalence rate of abnormal MoCA scores (85%). Participants using metformin had worse performance in MoCA (scores <26). Increased duration of metformin intake leads to a decline in MoCA performance.

**Data availability**

**Underlying data**

Dryad: Is metformin the only culprit for cognitive impairment in diabetes?, https://doi.org/10.5061/dryad.wpzgmsbrr.19

This project contains the following underlying data:

- Thesis_stats_final.xlsx
Extended data

Dryad: Is metformin the only culprit for cognitive impairment in diabetes?, [https://doi.org/10.5061/dryad.wpzgmsbrs](https://doi.org/10.5061/dryad.wpzgmsbrs).

This project contains the following extended data:

- MoCA_Availability.docx

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

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References


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