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# Mild cognitive impairment among patients with diabetes in Tabuk City, the Kingdom of Saudi Arabia and its relation to glycaemic control: A case-control study

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## RESEARCH

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## ABSTRACT

### Background
There is an increasing awareness regarding the interaction between diabetes mellitus and mild cognitive impairment (MCI), no researchers have assessed mild cognitive impairment among patients with diabetes in Saudi Arabia.

### Aims
The current study aimed to assess mild cognitive impairment among patients with diabetes mellitus in Tabuk, Saudi Arabia.

### Methods
A case-control study was conducted among 106 patients with diabetes mellitus, and 96 control subjects attending a diabetes center in Tabuk City, Saudi Arabia during the period from December 2018 to September 2019. The participants were invited to sign a written informed consent and then interviewed using a questionnaire based on the Montreal Cognitive assessment, demographic data, and cardiovascular risk factors. The ethical committee of the University of Tabuk approved the research and the Statistical Package for Social Sciences was used for data analysis. A P-value of <0.05 was considered significant.

### Results
There were 106 patients with diabetes mellitus and 96 control subjects matched for age and sex. MCI was evident in 50.9 per cent of patients with diabetes *vs.* 8.9 per cent of control subjects with a highly significant statistical difference (*P*<001, 95CI, 3.33–33.93), hypertension, overweight/obesity, coronary artery disease, and dyslipidaemia were commoner among patient with diabetes compared to their counterparts. A positive correlation was observed between mild cognitive impairment and hypertension (*P*<0.05, Wald, 7.649, 95 per cent CI, 018-.506). No correlation was found between MCI, duration of diabetes, and other cardiovascular risk factors.

### Conclusion
More than half of patients with diabetes in Tabuk City had MCI and is correlated with hypertension. Raising awareness about the effects of high blood pressure on cognitive function is needed.

### Key Words
Mild cognitive impairment, diabetes mellitus, HbA1c

## What this study adds:

**1. What is known about this subject?**

Cognitive impairment is common among patients with diabetes Mellitus and may negatively affect the glycaemic control. The extent of mild cognitive impairment among patients with diabetes is unknown in the Kingdom of Saudi Arabia.

**2. What new information is offered in this study?**

Mild cognitive impairment is prevalent among patients with diabetes mellitus and is correlated with hypertension.

**3. What are the implications for research, policy, or practice?**

Screening for mild cognitive dysfunction among patients with diabetes mellitus and treat in a timely related manner when appropriate. Raising the awareness about deleterious effects of hypertension in general and on cognitive function in particular.

## Background

Diabetes mellitus is a global health concern; the disease is rapidly growing especially in the Middle East due to economic development, urbanization, and shifting lifestyles including obesogenic diets and work involving physical inactivity.[1] In the Kingdom of Saudi Arabia, the situation is alarming, a threefold increase was observed during the period 1992-2010 (the figure jumps from 0.9 million to 2.5 million). Currently, 31.6 per cent are affected.[2,3] Some animal and human studies have linked Alzheimer's disease (AD) to type 2 diabetes mellitus. Although, the interrelational mechanisms are unclear, however, vascular defects were suggested as a link between cognitive impairment observed among patients with type 2 diabetes. An overlap is suggested between these two highly prevalent disorders that are highly associated with mortality and morbidity.[4] A piece of substantial evidence is that cognitive impairment among patients with type 2 diabetes starts in middle age or even in the prediabetes stage. Moreover, some authors[5] suggested a reversed hypothesis (cognitive decline precedes hyperglycaemia).

Dementia is highly prevalent worldwide, currently, 47 million people are affected and the number is expected to triple by the year 2050. Most people with dementia (two thirds) occur in low and middle-income countries with limited financial resources and less developed social and healthcare systems. Screening the at-risk including patients with diabetes mellitus may reduce the burden and cost of this common morbid disease due to the absence of a curative treatment at present. However, polyphenols were shown to be protective.[6,7] Also, the earlier detection of mild cognitive impairment will help to tailor oral hypoglycaemic medications to reduce the risk of hypoglycaemia especially among elderly patients with diabetes.[8] The relationship of diabetes mellitus and cognitive decline is bidirectional, it is observed that cognitive function at age eleven years predicts the glycated haemoglobin and cognitive function at 70 years.[5] Also, mild cognitive impairment may substantially affect well-being and diabetes management.[8] The pathophysiology of mild cognitive dysfunction includes insulin resistance and amyloid, hyperglycaemia, hypoglycaemia, and vascular disease,[9] Diabetes mellitus and cognitive decline when present together exacerbate each other deleterious consequences. Investigating the relationship between diabetes and cognitive dysfunction is crucial for the development of prevention strategies targeting both disorders. Thus we conducted this survey. In the current study, we assessed mild cognitive impairment among patients with type2 diabetes mellitus in Tabuk, Saudi Arabia.

## Method

This case-control study was conducted at the diabetes center in King Fahd Specialist Hospital, Tabuk, Saudi Arabia during the period from December 2018 to September 2019. The diabetes center is one of two centers providing secondary care for patients with diabetes in Tabuk and receiving a referral from Primary Healthcare Centers and other hospitals in the region. One hundred-six patients with type 2 diabetes and ninety-two age and sex-matched controls (randomly chosen from the co-patients to minimize socioeconomic differences) were approached. Patients with type 1 diabetes, pregnant ladies, severely ill patients, patients with stroke, and Parkinson's disease were not included as were patients with visual or hearing impairment who are not able to fill the questionnaire.[10] Participants were invited to sign a written informed consent, then a trained data collectors (a family physician and a diabetes educator who received three education training sessions on how to fill the questionnaire) interviewed the participants to collect demographic data, cardiovascular risk factors including hypertension, dyslipidaemia, and the level of exercise. Diabetes complications were also collected, the most recent glycated haemoglobin was reported from the patient's records to assess the degree of glycaemic control. The weight in Kg and Height in cm was measured to calculate the body mass index (BMI). The Arabic version of the Montreal Cognitive Assessment Questionnaire has been previously validated for use among patients with diabetes mellitus.[11] Montreal cognitive impairment assessment tool

was chosen because it better meets the criteria for mild cognitive impairment detection among patients over 60 years of age than other screening tests and is highly reliable in low-educated populations.[12,13] It is a thirty question test that takes 10–12 minutes to complete, the questionnaire evaluates different types of functional abilities including orientation (the date, month, year, day, place, and city), short-term memory by asking to repeat five words twice, then the participant is asked to repeat the same at the end of the task, a clue about the word category is given if the participant is not able to recall, executive function/visuospatial ability is tested by a trail test which requires the patient to draw a line to correctly sequence alternating digits and numbers and draw a cube, the participant is also asked to repeat two sentences correctly and then list all the words that begin with the letter F (language test). Abstraction is tested by asking how two items are alike (such as a train and a bicycle), three animal naming is another category of the questionnaire as is a Clock drawing test in which the patient is asked to draw ten past eleven. Attention is evaluated by asking the test tracker to repeat a series of numbers forward and then a different series backward. A score of 22.1 is considered as mild cognitive impairment.[14,15] Patients whose education is less than twelve years are given an extra one mark.

The ethical committees of both the University of Tabuk and the Directorate General of Tabuk Health Affairs approved the research.

The Statistical Package for Social Sciences (IBM, SPSS, version 20, Chicago) was used for data analysis. The Chi-square, independent t-test was used to test the statistical significance when appropriate. Logistic regression analysis was applied to test the relationship of mild cognitive impairment to vascular risk factors. The data were presented as percentages and mean± SD, a P-value of <0.05 was considered significant.

## Results

There were 106 patients with diabetes mellitus and ninety-two control subjects matched for age and sex. (age, 51.18±10.79 years *vs.* 49.32±5.51, P=0.272, and 52.8 per cent *vs.* 37.3 per cent were women, P=0.252). The numerically higher males among patients with diabetes (52.8 per cent *vs.* 37.3 per cent in comparators will not substantially affect the results, P=0.252). It is interesting to note that, mild cognitive impairment was found in 50.9 per cent of patients with diabetes *vs.* 8.9 per cent of control subjects with a highly significant statistical difference, P=0.000, 95CI, 3.33-33.93. In the current survey, hypertension was observed in 48.1 per cent of patients and 8.7 per cent of control subjects with a highly significant statistical difference, P=0.000, and 95 per cent CI, 3.06–30.98, coronary artery disease was reported in 22.2 per cent of patients and not found among control subjects, P=0.000, 95 per cent CI, 0.67–0.89, while dyslipidaemia was reported by 57.4 per cent of patients with diabetes and 6.5 per cent of control subjects with a highly significant statistical difference, P=0.000, 95CI, 5.32–70.09, no significant statistical difference was observed between patients and control subjects regarding the level of exercise, P=0.649, and 73.1 per cent of patients with diabetes were either overweight or obese with a highly significant statistical difference, P=0.032, 95CI, 1.07–5.77 Table 1. The higher rates of cardiovascular risk factors were not translated into a higher MCI except for hypertension.

In the present study mild cognitive total score was higher among control subjects compared to patients with type 2 diabetes with a highly significant statistical difference, 30.89±5.85 and 24.79±7.12 respectively, P=0.000, the visuospatial score was higher among control subjects that their counterparts with diabetes mellitus with a highly significant statistical difference, 4.50±0.89 and 3.37±1.40 respectively, P=0.000, the same applies for attention, 4.67±1.40 *vs.* 3.50±1.98, P=0.001 Table 2, depicted other mild cognitive score components.

Regarding the relationship of mild cognitive impairment to patients' characteristics, hypertension was positively correlated with MCI, P=0.006, Wald=7.649, 95 per cent CI=018-0.506, no correlation was evident between MCI and the glycated haemoglobin, P=0.159, Wald=1.985, 95CI=0.447–1.141. Table 3, illustrated the correlation of MCI to other different parameters.

## Discussion

In the current study, mild cognitive impairment was found in 50.9 per cent of patients with diabetes mellitus (95 per cent CI, 3.33–33.93), the present findings were in agreement with a study conducted in India[16] and found a rate of 50.5 per cent among patients with diabetes mellitus. The current finding of higher females among patients with MCI is similar to Yerrapragada et al.[16] who observed that women outmoded males. The result of MCI found in the present survey is higher than a prevalence reported among elderly population with diabetes in China[17] (28.3 per cent (95 per cent CI: 23.5–33.2), plausible explanations could be the more cardiovascular risk factors observed in the present study, also the different methods of MCI assessment may explain the discrepancies. Furthermore, all the participants

with diabetes mellitus in the present study had poor glycaemic control (with a higher numerical value among patients with MCI, data not shown) putting them at a higher degree of complications. Physicians may need to prevent, early identify, and treat MCI. Another study published in China[18] reported a prevalence of 21.8 per cent, the researchers found a lower score of neuropsychological tests among patients with diabetes compared with their counterparts without the disease in similarity to the current findings in which all the components of Montreal Cognitive Assessment scored lower among patients with diabetes. The relationship between the components of metabolic syndrome and MCI is controversial with some reported an association.[19] However; some studies showed a lack of association, in the present study, hypertension, Dyslipidaemia, and overweight/obesity were higher among patients with diabetes compared to controls. Besides, only hypertension was positively correlated with MCI in contrast to body mass index, dyslipidaemia, and HbA1c. A recent study that analysed two cohorts and published in Denmark[20] showed that diabetes mellitus is associated with dementia; however, high glycated haemoglobin is associated with dementia in one cohort but not in the other. In the present survey, no relationship was found between mild cognitive impairment and HbA1c. The pathogenesis of dementia is multi-factorial with different pathogenesis pathways; each may be specific to a component of metabolic syndrome. Examples are neuroinflammation and adipokine imbalance mediated by a high body mass index and central insulin resistance and hypoglycaemia in diabetes A recent study[21] assessed white matter hyperintensities (marker of cerebral small vessel diseases) and concluded that hypertension is associated with the severity of white matter hyperintensities, the current study showed that high blood pressure was positively correlated with mild cognitive impairment supporting the previous observations. Liu et al.[17] stated that the duration since the diagnosis of diabetes mellitus and the glycated haemoglobin were significantly associated with mild cognitive impairment among patients with diabetes in contradiction to the present findings, the discrepancy can be explained by the fact that type 2 diabetes mellitus could be silent. Thus, the time of diagnosis may greatly be varied in different countries and the fact that all the patients with diabetes mellitus in the current survey had poor glycaemic control. The current data found no correlation between a high body mass index and MCI, our findings were similar to Li[22] and colleagues who assessed the interactive relations of type 2 diabetes and abdominal obesity to cognitive impairment and found that the waist circumference is associated with MCI but not obesity alone.

The limitations of the present study were the relatively small size of the study group, the fact that the study was conducted at a single diabetes center, so generalization to other places cannot be insured. Also, we did not control for various confounders including smoking and socioeconomic status.

## Conclusion

Mild cognitive dysfunction was prevalent among patients with diabetes mellitus in Tabuk, Saudi Arabia. Hypertension was found to be correlated with mild cognitive impairment. No correlation was evident between MCI, dyslipidaemia, obesity, and coronary artery disease, and the duration since the diagnosis of diabetes mellitus. Measures to control high blood pressure among patients with diabetes mellitus are urgently needed. Further multi-center studies investigating the systolic and diastolic blood pressure and controlling for confounders including the level of education, smoking, socioeconomic status, and depression are recommended.

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## PEER REVIEW

Not commissioned. Externally peer reviewed.

## CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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## ETHICS COMMITTEE APPROVAL

The current survey was approved by the ethical committee of the University of Tabuk, Saudi Arabia (Ref. Number-UT-72-24-2018, date: 17/12/2018).

**Table 1: Comparison between patients with diabetes mellitus and control subjects**

| Character | DM | Control | P-value | 95% CI |
|---|---|---|---|---|
| Sex<br>Males<br>Females | <br>50 (47.2%)<br>56 (52.8%) | <br>54 (62.7%)<br>38 (37.3) | 0.252 | 0.283-1.39 |
| Mild cognitive impairment | 54 (50.9%) | 8 (8.9%) | <0.001 | 3.33-33.93 |
| Hypertension | 52 (48.1%) | 8 (8.7%) | <0.001 | 3.06-30.98 |
| Coronary artery disease | 24 (22.2%) | 0 (0.00%) | <0.001 | 0.67-0.89 |
| Dyslipidaemia | 62 (57.4%) | 6 (6.5%) | <0.001 | 5.32-70.09 |
| Level of exercise | 34 (31.5%) | 30 (32.6%) | 0.649 | |
| Overweight/obese | 76 (73.1%) | 48 (52.2%) | 0.032 | 1.07-5.77 |
| Age (mean± SD | 51.18±10.79 | 49.32±5.51 | 0.272 | |

*Chi-square test

**Table 2: The different shades of mild cognitive impairment among patients and control subjects***

| Character (mean± SD) | DM | Controls | P-value |
|---|---|---|---|
| Visuo-spatial and Executive | 3.37±1.40 | 4.50±0.89 | <0.001 |
| Animals naming | 2.88±0.37 | 3.00±00 | 0.044 |
| Attention | 3.50±1.98 | 4.67±1.40 | 0.001 |
| Language | 1.89±0.93 | 2.23±0.66 | 0.010 |
| Abstraction | 0.96±0.93 | 1.10±0.94 | 0.443 |
| Delayed recall | 2.64±2.21 | 4.39±1.25 | <0.001 |
| Orientation | 5.84±0.36 | 5.97±1.47 | 0.026 |
| Total score | 24.79±7.12 | 30.89±5.85 | <0.001 |

*Independent-Sample T-Test

**Table 3: The relationship of mild cognitive dysfunction to the duration since diabetes diagnosis, HbA1c, body mass index (BMI), hypertension, Coronary syndrome, and dyslipidaemia***

| Character | B | SE. | Wald | df | Sig. | Exp. (8) | 95% CI for Exp. |
|---|---|---|---|---|---|---|---|
| Duration of DM | 0.007 | 0.036 | 0.040 | 1 | 0.842 | 1.007 | 0.938-1.081 |
| HbA1c | -0.337 | 0.239 | 1.985 | 1 | 0.159 | 0.714 | 0.447-1.141 |
| BMI | 0.009 | 0.043 | 0.041 | 1 | 0.840 | 1.009 | 0.927-1.098 |
| HRT | -2.336 | 0.844 | 7.649 | 1 | 0.006 | 0.097 | 0.018-.506 |
| Coronary artery | -0.360 | 0.973 | 0.137 | 1 | 0.711 | 0.697 | 0.104-4.693 |
| disease | 0.073 | 0.811 | 0.008 | 1 | 0.928 | 1.076 | 0.220-5.270 |
| Dyslipidemia | 4.161 | 2.392 | 3.026 | 1 | 0.082 | 64.140 | |
| Constant | | | | | | | |

*Logistic regression analysis