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Investigation on the relationship between diabetes mellitus type 2 and cognitive impairment

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ARTICLE INFO

ABSTRACT

Objective: The incidence of cognitive impairment is increasing with age; however, little is known about the role of hyperglycemia in cognitive impairment. This study focuses on investigating the relationship between diabetes mellitus type 2 and cognitive impairment.
Methods: 60 diabetic patients, amongst whom, 30 had a well-controlled diabetes status and the other 30 had not. These patients were compared to 60 non-diabetic controls whose age, sex and educational class matched with the individuals of the first group. Patients with important risk factors for cognitive disorders (renal failure, major depressive disorders and psychoactive drug users, cerebrovascular accident history, etc.) were not included in the study. Modified Mini Mental Status examination (mMMSE) was done for all patients by a blinded expert examiner.
Results: Subjects with diabetes ($n = 60$) had lower MMSE score than those without diabetes ($P < .01$). Diabetes was also associated with increased odds of cognitive decline as determined by MMSE scores (odds ratio = 1.9; CI = 95%, 1.01–3.6). A significant correlation between duration of disease and cognitive dysfunction was observed, $P = 0.001$. Also, the same correlation was found for quality of diabetes control, $P = 0.002$.
Conclusion: Diabetes mellitus is associated with lower levels of cognitive function.

1. Introduction

The worldwide incidence and prevalence of diabetes mellitus (DM) is increasing, due almost exclusively to an increase in non-insulin dependent (type 2) DM, which represents more than 90% of all cases of diabetes. Presently, there is a global pandemic of type 2 DM and its clinical sequel [1].

Diabetes mellitus not only causes somatic complications but also may result in accelerated cognitive dysfunction.

Dementia and cognitive decline are among the most common and most feared conditions of old age, making the identification of modifiable risk factors for dementia, an urgent public health priority [2].

A recent study with the purpose of verifying whether borderline diabetes may increase the risk of dementia and (Alzheimer's disease) AD, has been carried out on 1173 dementia- and diabetes-free individuals of age 75 or over. Subjects were examined longitudinally, for three times in order to identify the ones with dementia and AD. Borderline diabetes was defined as a random plasma glucose level of 7.8–11.0 mmol/L. During a 9-year follow-up, 397 subjects developed dementia, including 307 Alzheimer's cases. At the baseline, 47 subjects were identified with borderline diabetes. Borderline diabetes was associated with adjusted hazard ratios (95% CIs) of 1.67 (1.04–2.67) for dementia and 1.77 (1.06–2.97) for AD. Finally, the researchers come up with this

conclusion that, borderline diabetes increases risks of dementia and Alzheimer's disease and the risk effect is independent of the future development of diabetes [3].

There is a growing interest in preclinical transitional states of AD as targets for treatment and prevention. Mild cognitive impairment (MCI), and particularly amnestic MCI, has been described as a transitional state between normal cognition and AD that is increasingly used in clinical and research settings [4].

Extensive research on the effects of diabetes on cognitive function in old age has provided mixed findings. Although the majority of the studies have found negative effects on cognitive functioning related to diabetes, several studies have reported no relationship [5].

In a cross-sectional study of citizens, aged 75, 80, or 85 years, Croxson et al. obtained a mental status examination and an oral glucose tolerance test on 239 individuals. Among the 31 patients, the proportion with low cognitive function did not differ significantly from that for normal individuals [6]. By contrast, Katzman et al. reported a significant association between self-reported diabetes and dementia in a case-control study of 434 healthy volunteers aged 75–85 years followed over a 5-year period [7].

Iran is also a country with high prevalence of diabetes mellitus, but investigation of the relationship between diabetes mellitus and cognitive impairment has not been reported. The aim of this investigation is to reveal the relationship between diabetes mellitus type 2 and cognitive impairment by a cross-sectional population based study.

2. Materials and methods

Our study is a cross-sectional one and started in January 2005 in Shahid Beheshty General Hospital and Golabchi Diabetes Center, Kashan, Iran.

After reviewing patients' medical records, we selected type 2 diabetics according to American Diabetes Association criteria for diagnosis of diabetes mellitus , fasting plasma glucose (FPG) at or above 126 mg/dL (7.0 mmol/L), a 2-h value in an oral glucose tolerance test (OGTT) at or above 200 mg/dL (11.1 mmol/L), or a random (or "casual") plasma glucose concentration 200 mg/dL (11.1 mmol/L) in the presence of symptoms and the diagnosis of diabetes must be confirmed on a subsequent day by measuring any one of the three criteria [8]. To determine type 2 DM, patients must have been diagnosed in the 3rd or later decades of their life and had no history of diabetic ketoacidosis.

Diabetic patients were under treatment with oral hypoglycemic agents, glyburid and metformin in various dosages and other non-pharmacologic strategies have been used by most cases including diet control and physical exercise.

Education-wise, we divided the individuals into three classes, according to the number of years which they had attended school. Classes are: low class (<5 years), middle class (5–12 years) and high class (>12 years).

All cases with cognitive dysfunction caused by reasons other than hyperglycemia were excluded from study. However, patients who have been under treatment with psychoactive/depressant drugs (anticholinergics, narcotics, antidepressants, benzodiazepines, or major tranquilizers), any cerebrovascular accident history and presence of major depressive symptoms were excluded. Complicated hypertensions (cerebrovascular accidents, multiinfarct dementias, renal failure, etc.) or patients with uncontrolled prolonged hypertension were also excluded from our study.

Type 2 DM emerges several years before the diagnosis. For this, we defined "Disease duration" to be the time span between diagnosis of diabetes mellitus and the MMSE examination.

Based on glycemic measures in regular follow-up examinations in the latter months of this study, diabetic patients were divided into two groups, "well-controlled": FPG less than 120 mg/dL and 2 h post prandial plasma glucose less than 180 mg/dL and hemoglobin A1c $\leq$ 7%), and "poorly controlled": hemoglobin A1c $\geq$ 9%.

From each group (well-controlled and poorly controlled), 30 patients were selected consecutively, making up a total of 60 diabetic patients. As control, 60 non-diabetics were selected from individuals, referred to our clinic for other reasons like periodic medical check-up, screening for DM, control of hypertension and etc. All of them were evaluated for DM by FPG and OGTT and like DM patients; cases which had any causes with any cognitive impairment were excluded. Selection for control group was also done consecutively and their age, sex and education levels conform to those of diabetic cases.

Then each one from case and control group evaluated for cognitive function by a neurologist expert in the field of dementia and was blinded to subjects of study groups. The instrument used, was the modified Mini Mental Status Examination (MMSE) Questionnaire. This test was introduced as a standard measure of cognitive function to be used for both research and clinical purposes. A score of less than 24 considered to be consistent with a cognitive impairment/dementia [9]. Scores of 20–23 considered as to have mild cognitive impairment, 10–19 moderate and 0–9 severe impairment.

3. Statistical analysis

The Chi-square test was applied to test differences in proportions of qualitative variables and continuous variables were analyzed using Student's t-test, with 5% level of significance.

Mean score of MMSE compared between control and case groups, using Student's t-test (two sample equal variance and two tailed distributions). Also, this score compared between well-controlled and poorly controlled DM patients using the same test. Using Chi-square test, groups were compared for evidence of cognitive impairment and its severity as well as the association between cognition and DM control quality.

Logistic regression was applied to find the relationship between some characteristics of diabetes mellitus and cognitive impairment.

4. Results

A total of 120 cases were studied, 60 type 2 DM patients as case group and 60 non-diabetics as control with mean age of

49.9 ± 7.9 years (range 30–75 years). There were 32 (53.3%) male and 28 (46.7%) female in DM group and 34 (56.7%) male and 26 (43.3) female in control non-DM group ($P = 0.71$). Mean age was 49.5 ± 8.3 years in DM group and 50.18 ± 7.52 years in non-DM group ($P = 0.67$). Mean duration of disease in DM group was 8.45 ± 3 years.

Serum HbA1c level was high in all poorly controlled cases. Also, their blood glucose, both in fasting and random checks, was high. Mean serum HbA1c was 6.09 ± 0.53 for the well-controlled group and 10.26 ± 0.59 for poorly controlled group.

Twenty (33.3%) diabetic patients and 15 (25%) control subjects suffered from hypertension (d.f. = 1, $p < 0.31$). Educational status of subjects is as follows: in diabetics 16 (26.7%) cases were in low level, 40 (66.7%) diabetics were in medium level and 4 (6.7%) cases had higher educations. These were 14 (23.3%), 39 (65%) and 7 (11.7%) respectively in control group ($P = 0.62$).

Disease duration was significantly longer in patients whose DM control was not adequate. Mean duration of disease was 6.9 ± 2.7 years for patients with good control and 10 ± 2.66 years in poorly controlled diabetics (CI = 95%, −1.7 to −4.5, $p < 0.0001$).

From 60 diabetics, 21 (35%) cases had cognitive impairment (i.e. MMSE score of less than 24). In non-diabetics, cognitive impairment was detected only in 11 (18.3%) out of 60 cases which is significantly lower than the frequency of cognition impairment in DM group ($p = 0.038$, CI = 95%, $1.01 < OR = 1.9 < 3.6$).

Mean of MMSE scores of subjects was 27.16 ± 2.72 (range 20–30). This score was 28.25 ± 2.38 for non-diabetics and 26.07 ± 2.6 for diabetics. Statistical analysis showed a significant difference between MMSE score of two groups ($P = 0.001$). Cognitive impairment was in mild level in both groups and there were no moderate or severe cases (Table 1).

As stated earlier, there were two subgroups within the diabetics, namely, the ones with well-controlled DM and the ones with poorly controlled DM and both matched in age, sex

Table 1 – Characteristics of diabetic and non-diabetic group and comparison of cognitive state in both			
	Diabetes (number = 60)	Non-diabetes (number = 60)	P value
Sex			P = 0.71
Male	32 (53.3%)	34 (56.7%)	
Female	28 (46.7%)	26 (43.3)	
Age (mean, years)	49.5 ± 8.3	50.18 ± 7.52	P = 0.67
Education state			P = 0.62
Low level	16 (26.7%)	14 (23.3%)	
Medium level	40 (66.7%)	39 (65%)	
High level	4 (6.7%)	7 (11.7%)	
Cognitive impairment			P = 0.038
Yes	21 (35%)	11 (18.3%)	
No	39 (65%)	49 (81.7%)	
Mild	19 (31.6%)	10 (16.7%)	
Moderate	2 (3.33%)	1 (1.67%)	
Severe	0	0	
MMSE score	26.07 ± 2.6	28.25 ± 2.38	P = 0.001

Table 2 – Characteristics of good controlled and poor controlled diabetics and comparison of cognitive state in both			
	Good control (number = 30)	Poor control (number = 30)	P value
Sex			P = ns
Male	16 (53%)	16 (53%)	
Female	14 (47%)	14 (47%)	
Age (mean, years)	50.4 ± 8.31	48.7 ± 8.41	P = 0.43
Educational states			P = ns
Low level	8 (26.3%)	8 (26.3%)	
Medium level	20 (66.3%)	20 (66.3%)	
High level	2 (6.3%)	2 (6.3%)	
Cognitive impairment			
Yes	8 (24.3%)	13 (40%)	
No	22 (75.7%)	17 (60%)	P = 0.176
MMSE score	27.07 ± 2.71	25.07 ± 2.1	P = 0.002

and education. Mean score of MMSE was 27.07 ± 2.71 in well-controlled and 25.07 ± 2.1 in poorly controlled patients ($P = 0.002$). This shows a significant MMSE score difference in well-controlled and poorly controlled DM. However, in comparing these two groups for presence of cognitive impairment, there was not significant evidence of a difference between poorly controlled and well-controlled DM as: in poorly controlled and well-controlled groups, 13 (40%) and 8 (24.3%) patients suffered from cognitive impairment and 17 (60%) and 22 (75.7%) did not, respectively ($P = 0.176$) (Table 2).

Twenty-one (35%) diabetics with cognitive impairment had mean disease duration of 9.9 ± 2.9 years and 39 (65%) patients without cognitive impairment had mean disease duration of 7.64 ± 2.78 years. Statistical analysis shows that there is a significant difference in the disease duration for diabetic patients with or without cognitive impairment. It is evident that the disease duration is remarkably longer in patients with cognitive impairments than the ones without such disorders ($P = 0.004$). Also Pearson's correlation coefficient shows negative correlation between disease duration and cognitive impairment ($R = −0.408$, $P = 0.001$) (Fig. 1).
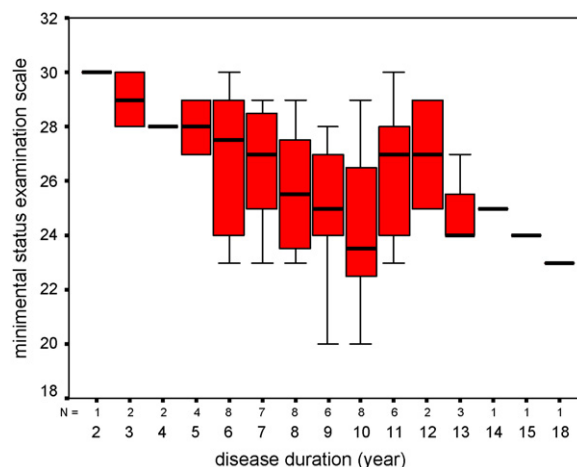

Fig. 1 – Correlation between disease duration and MMS score.

5. Discussion

Controversial results have been reported about the status of diabetes mellitus as a risk for mental impairment.

To determine whether diabetes is related to a higher risk of mild cognitive impairment, during a longitudinal cohort study, Luchsinger et al., studied 918 of 1772 participants without prevalent MCI or dementia at baseline and with at least 1 follow-up interval. Diabetes was related to a significantly higher risk of all-cause MCI and amnestic MCI after adjustment for all covariates. Diabetes was also related to a higher risk of non-amnestic MCI, but this association was appreciably attenuated after adjustment for socioeconomic variables and vascular risk factors [4].

In our study, regardless of a small number of participants and a different method and scale in determination of MCI, yet we found a higher prevalence of MCI in diabetic group.

Allen et al. arranged a literature search and evaluated 10 studies (nine population-based and one of case-controlled design) that included a definable diabetic population and assessments of cognitive function at baseline and at follow-up. These 10 studies utilized a combination of domain-specific cognitive assessments and a clinical diagnosis of dementia in the assessment of cognitive function. Diabetes was associated with either an accelerated cognitive decline or an increased incidence of dementia in eight over nine of the population-based studies [10].

Yaffe et al. investigated the association between diabetes and impaired fasting glucose and cognition and risk of developing both dementia and mild cognitive impairment in older women. They analyzed data from a 4-year randomized trial of raloxifene among 7027 women at 178 sites. The main outcome was baseline and 4-year change on standardized cognitive tests and risk of developing clinically significant cognitive impairment. There was greater 4-year decline among diabetics ($P = 0.001$), and further adjustment for education, race, and depression led to similar results [11]. Similarly, in a cross-sectional study of 462 men aged 69–89 years, diabetic individuals scored significantly lower on the MMSE than men with normal glucose tolerance; among non-diabetic individuals, those with higher insulin levels made more errors than those with lower levels [12].

However, similar results have not been found in some studies. There was no relationship between type 2 diabetes and cognitive function in the Rancho Bernardo cohort study which measured by 10 tests [13]. Considering our findings regarding the duration of diabetes, one explanation may be the predominance of recently diagnosed diabetes in that cohort: most of their participants had diabetes for 3 years whereas the mean duration of disease of our diabetics was 8.45 years.

Our conclusion that, longer duration of disease seems to be related to cognitive dysfunction is consistent with other studies. Gregg et al. showed increasing risk of cognitive decline with increasing duration of diabetes [14]. Also, it was showed that each 5-year increment between diabetes diagnosis and cognitive assessment was associated with lower scores on tests of logical memory, word fluency, and similarities [15].

Small treatment studies have found that administration of oral hypoglycemic agents to non-demented patients with type 2 diabetes resulted in improved performance on cognitive tasks [16]. Interestingly, in the study of osteoporotic fractures [14] and the Framingham study [15], insulin treatment was related to poorer cognitive performance, and in the Framingham study, diabetic patients treated with oral medications or diet performed similarly to non-diabetic patients. Unfortunately, we did not have enough patients using insulin to compare oral hypoglycemic agents and insulin effects on cognitive function but in overall we found a significant correlation between quality of diabetes control and cognitive dysfunction ($P = 0.002$, Table 2).

Recently, Ryan et al. evaluated the effects of improvements in metabolic control on the cognitive dysfunction associated with type 2 diabetes. Their randomized double-blind trial enrolled 145 subjects at 18 centers in the United States. Cognitive function was assessed at baseline and week 24 using the Digit Symbol Substitution Test, the Rey Auditory Verbal Learning Test, and the Cambridge Neuropsychological Test Automated Battery. Working memory improved with both rosiglitazone ($P < 0.001$) and glyburide ($P = 0.017$). Cognitive improvement was significantly correlated with improved glycemic control as measured by FPG. They concluded that the magnitude of cognition improvement is correlated with the degree to which FPG improved. According to their results a cognitive benefit is achievable with pharmacological interventions targeting glycemic control [17].

Based on our study, one might conclude that type 2 diabetes is related to poor performance on cognitive function and good control of disease seemed to lower this disability and this could result to poorer ability in diabetes self-care and greater dependency. For above mentioned reasons, routine screening of cognition in diabetics is recommended. Because both diabetes and poor cognitive function are common conditions especially among elderly individuals, further investigations are warranted for clear understanding of subject.

6. Conclusion

In the present study we evaluated the effect of diabetes mellitus on Cognitive impairment. We compared prevalence of cognitive impairment in diabetic and non-diabetic group, matched in age, sex and educational state. According to our findings, cognitive impairment was mild in both groups and prevalence was nearly two times in diabetic patients. In diabetic group, poor controlled DM had a lower MMSE scores than good controlled DM. There was a negative relationship between duration of disease and MMSE scores but not in prevalence of cognitive impairment.

Conflict of interest

There are no conflicts of interest.

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