

Relationship of Cognition, Depression and Anxiety to Glycemic Control in Older Adults with Diabetes

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Received 5 April 2014; revised 5 May 2014; accepted 15 May 2014

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Abstract

Objective: This study aimed to assess the relationship of cognition, depression and anxiety to glycemic control in elders with diabetes. DM is a chronic medical condition. Its control depends on adherence to medical therapy and making decisions related to lifestyle changes. This decision making capacity is affected by many factors including cognition and psychological status. **Design:** It was a case control study. **Setting:** It was done in Ain Shams University Hospital inpatients and DM outpatient clinic, Cairo, Egypt. **Participants:** Of the one hundred diabetic patients aged ≥ 60 years, 50 had Hemoglobin A1c (HbA1c) ≥ 7.5 (cases) and 50 had Hb A1c < 7.5 (controls). **Measurements:** Cognition was assessed using minimal status examination (MMSE) test, Mattis Organic Mental Syndrome Screening Examination (MOMSSE) and Cambridge Cognitive Examination (CAMCOG) test. Geriatric depression scale-15 (GDS-15) was performed for depression assessment, while anxiety was assessed by DSM IV criteria. Laboratory investigations included: fasting blood sugar (FBS), post-prandial blood sugar (PPBS), glycated haemoglobin (Hb A1c), low density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and triglycerides (TG). **Results:** Significant difference was found between the two groups regarding scores of cognitive tests: MMSE score ($p = 0.004$); below average ($p = 0.02$) and average scores ($p = 0.05$) of MOMSSE; CAMCOG score ($p = 0.015$); and CAMCOG divided items score including orientation ($p = 0.003$), comprehension ($p = 0.005$), expression ($p = 0.020$), attention ($p = 0.002$), and abstraction ($p = 0.008$) as well as depression screening scores ($P = 0.002$). Using Receiver Operating Characteristic, CAMCOG had better sensitivity and MOMSSE had better specificity. **Conclusion:** Cognitive impairment was associated with poor glycemic control, and impairment in attention and abstraction, related to executive function, functions were found to be associated with poor glycemic control. These functions may be more needed in self management of DM and hence affected glycemic control. Depression was associated with poor glycemic control but anxiety was not.

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Keywords

Diabetes Mellitus, Cognition, Depression, Anxiety, Hb A1c, Elders

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome [1].

DM in older adults has become a major public health problem affecting an increasing number of individuals worldwide. Glycemic control is an essential element of DM management. It is failed to be achieved or maintained by many older adults [2]. Effective glycemic control involves many steps including proper nutrition, regular exercise, self monitoring of blood glucose, and medication management [3].

Previous studies have confirmed that both old age & DM are independently associated with an increased risk of cognitive dysfunction; the risk is even greater for older adults with DM [4]. Cognitive deficits in areas of psychomotor efficiency, global cognition, episodic memory, semantic memory, and working memory were noted in both young and older patients with DM [5]. Abnormalities in executive functions, including problem solving, planning, organization, insight, reasoning, and attention, were noted in diabetics [6]. Diabetic patients are expected to suffer from difficulty in managing their disease due to cognitive dysfunction [6].

Not only cognitive dysfunction, but also previous studies reported significant association between psychiatric illnesses and poor glycemic control. Data on the relation between depression and anxiety and glycemic control in diabetic elderly patients are scarce. Depression comorbidity with DM has many hazards as it is a risk factor for poor metabolic control, decreased physical activity, and potentially more complications and functional impairment [7].

In addition, some authors suggest that anxiety comorbidity with DM has been associated with poor glycemic control, regimen adherence, and with accelerated rates of coronary heart disease [8].

Therefore, the aim of the current study was to assess the relationship of cognition, depression and anxiety to glycemic control in elders with diabetes.

2. Materials and Methods

2.1. Study Design and Setting

The study was a case control study. The study was carried out on diabetic elderly patients, aged 60 years or more, visiting the geriatric hospital inpatient and DM outpatient clinic of Ain Shams University Hospital, Cairo, Egypt. However, patients with impaired Mini-Mental Status Examination (MMSE) screening test, with a score less than 24 [9], delirium or hypoglycemia were excluded. One hundred patients were included in this study; 50 had Hemoglobin A1c (Hb A1c) ≥ 7.5 (cases) and 50 had Hb A1c < 7.5 (controls) [10]. Both cases and controls groups were cross matched regarding age and gender. The research was conducted over the period from October 2011 to October 2013. It was approved by the ethical Committee of Ain Shams University. Informed written or oral consent was taken from each participant and full confidentiality of the data collected was ensured to all participants.

2.2. Data Collection

All participants were subjected to complete medical history taking (including age, DM history, and history of

other co-morbidities). Each patient then underwent cognitive assessment by MMSE [9], its validated Arabic version was used [11], Mattis Organic Mental Syndrome screening Examination (MOMSSE) [12] and Cambridge Cognitive Examination (CAMCOG) [13], using its Arabic version [14], tests. Assessment of depression was done using geriatric depression scale-15 (GDS 15), normal GDS score is <5, [15] the Arabic version of the test was applied [16]. Assessment of anxiety was done using DSM-IV criteria [17]. Functional assessment was done by Activities of daily living (ADL) [18], Arabic version was used [19], and Instrumental activities of daily living (IADL) [20].

2.3. Laboratory Investigations

Each patient was instructed to fast 12 hours, venous blood sample was drawn from each participant into potassium EDTA tube; 5 ml was collected of venous blood by venipuncture. Serum was separated by centrifugation and was divided into 2 samples:

The first sample was used for measurement of fasting blood sugar.

The second sample was frozen at -20°C until assayed in the laboratory of clinical pathology department; Ain Shams University, Faculty of medicine. Serum level of low density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), and triglycerides (TG) were measured by enzymatic hydrolysis and oxidation.

A third sample of 2 ml was withdrawn by venipuncture 2 hours after eating. Centrifugation was done and serum was used for measurement of 2 hour postprandial blood sugar. Hb A1c was measured spectrophotometrically at the central laboratories of Ain Shams university hospital using (Biosystem, BTS-330, S.A. Costa Brava, Barcelona, Spain) spectrophotometer. Lipid profile was done in the central laboratory in Ain Shams University teaching hospital.

2.4. Statistical Analysis

Data were collected and analytical statistics were done using the 16th version of statistical package for social sciences (SPSS, Chicago, IL, USA). Qualitative data were presented in the form of frequency tables (number and percent). Quantitative data were presented in the form of means and SD.

Normality distribution of the variables was tested using one sample Kolmogorov Smirnov test. Regarding Quantitative data, differences between two groups were assessed using the Student's t test for parametric data or Mann Whitney U test for non-parametric data. Regarding qualitative data, the chi-square test or Fisher's Exact test was used to compare between the two groups.

Receiver operator curve (ROC) analysis was used to test the discriminatory power of anxiety, depression and cognitive tests in prediction of uncontrolled DM, with calculation for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). MedCalc 9.6.2.0 package (MedCalc Software, Mariakerke, East-Flanders, Belgium) was used to compare between area under the curves (AUCs) of cognitive tests for the prediction of uncontrolled DM.

The level of significance was taken at P value < 0.05.

3. Results

The mean age of all participants was 67.12 ± 6.36 years, the mean duration of DM was 9.96 ± 6.9 years, and the mean HbA1c was 8.2 ± 1.7 . Forty four percent of participants were males. A significant difference was found between ADL score, application of treatment, follow up status and glycemic control ($p < 0.001$ for all) (**Table 1**). There was no significant difference between the two groups regarding age and education adjusted MMSE ($p = 0.091$), but a significant difference exists regarding CAMCOG, MOMSSE below average and average status, and depression ($p = 0.015, 0.02, 0.05, \text{ and } 0.002$ consecutively) but no significant relation was found regarding anxiety ($p = 0.096$) (**Table 2**). **Table 3** showed significant difference between the two groups regarding orientation, comprehension, expression, attention and abstraction items of CAMCOG ($p = 0.003, 0.005, 0.020, 0.002$ and 0.008 consecutively). By ROC curve, the discriminatory power of adjusted MMSE and anxiety in prediction of uncontrolled DM was of poor accuracy (AUC = 0.58 and 0.57 consecutively), while other tests had AUCs > 0.60 (**Table 4**). Using MedCalc program to compare (AUCs) of MOMSSE versus CAMCOG revealed no significant difference ($P = 0.66$). However, CAMCOG had better sensitivity and MOMSSE had better specificity.

Table 1. Comparing studied groups as regard the age, gender, education, functional status and treatment status.

Variables	Controlled	Uncontrolled	P
Age	66.5 ± 5.6	67.7 ± 7	0.332
Male gender	25 (50%)	19 (38%)	0.227
Illiterate	19 (38%)	24 (48%)	0.31
Below high school	11 (22%)	13 (26%)	0.63
High school	4 (8%)	1 (2%)	0.15
Above high school	16 (32%)	12 (24%)	0.33
Functional status			
ADL	5.6 ± 1.4	4.1 ± 2.4	<0.001
IADL	7 ± 2.1	5.2 ± 3.2	0.001
Treatment			
Duration of diagnosis of diabetes*	9.8 ± 5.7	10.1 ± 7.9	0.818
Oral tab N(%)	28 (56%)	28 (56%)	0.548
Insulin	22 (44%)	25 (50%)	
Self	47 (94%)	32 (64%)	<0.001
Other person	3 (6%)	18 (36%)	
YES	40 (80%)	22 (44%)	<0.001
No	10 (20%)	28 (56%)	

Values were expressed in form of mean \pm SD for quantitative data and number (%) for qualitative data. ADL = activities of daily living, IADL = instrumental activities of daily living.

Table 2. Comparing the studied groups as regard cognitive and psychological status.

Variables	Controlled	Uncontrolled	P
Cognitive assessment			
Not impaired	37 (74%)	29 (58%)	0.091
Impaired	13 (26%)	21 (42%)	
CAMCOG	76.3 ± 18.1	66.7 ± 20.1	0.015
Below average	10 (20%)	25 (50%)	0.02
Average	22 (44%)	13 (26%)	0.05
Above average	18 (36%)	12 (24%)	0.19
Psychological assessment			
GDS15 (depressed)	7 (14)	21 (42)	0.002
Anxiety (anxious)	6 (10)	12 (24)	0.096
Laboratory results			
HbA1c	6.9 ± 0.5	9.5 ± 1.5	<0.001
FBS	116.7 ± 32.9	167.4 ± 49	<0.001
PPBS	161.1 ± 46.9	230 ± 45.8	<0.001
TC	145 ± 44.3	182.4 ± 56.1	<0.001
TG	122.3 ± 47.8	150.4 ± 66.4	0.017
LDL	88.2 ± 34.6	125.9 ± 47.9	<0.001
HDL	34.1 ± 11.3	31.2 ± 14.0	0.264

Values were expressed in form of mean \pm SD for quantitative data and number (%) for qualitative data. CAMCOG = Cambridge Cognitive Examination; FBS = Fasting Blood Sugar; GDS 15 = Geriatric depression scale-15; HbA1c = Glycated Hemoglobin; HDL = High density lipoprotein; LDL = Low density lipoprotein; MMSE = Minimental Status examination test; MOMSSE = Mattis Organic Mental Syndrome Screening Examination; PPBS = Post Prandial Blood Sugar; TC = Total Cholesterol; TG = Triglycerides.

There was no significant association between education and follow up status ($P = 0.052$) (data were not presented).

Table 3. Comparing studied groups as regard the CAMCOG divided items score.

CAMCOG	Groups						P-value
	Controlled			Uncontrolled			
	Mean	±	SD	Mean	±	SD	
Orientation	9.5	±	1.2	8.4	±	2.0	0.003
Comprehension	7.8	±	1.5	6.9	±	1.6	0.005
Expression	14.1	±	2.9	12.5	±	3.7	0.020
Recall	8.6	±	2.0	8.0	±	2.2	0.177
Recent memory	2.8	±	1.1	2.6	±	1.4	0.604
Remote memory	3.7	±	2.1	3.3	±	2.0	0.303
Attention	5.8	±	1.7	4.4	±	2.6	0.002
Praxis	9.1	±	2.8	8.0	±	3.0	0.065
Calculation	1.9	±	0.2	2.0	±	0.0	0.320
Perception	8.4	±	2.1	7.8	±	2.3	0.184
Abstraction	4.2	±	3.1	2.5	±	3.3	0.008

Values were expressed in form of mean \pm SD; CAMCOG = Cambridge Cognitive Examination.

Table 4. Sensitivity, specificity, positive predictive value (PPV), negative predicative vale (NPV) and accuracy of depression, anxiety and cognitive tests (adjusted MMSE, MOMSSE, CAMCOG).

	Sensitivity	Specificity	PPV	NPV	Accuracy (%)
Depression	42	86	75	59.72	64
Anxiety	---	----	----	----	57
MOMSSE	50	80	71.43	61.54	65
Adjusted MMSE	---	---	---	---	58
CAMCOG score	66	56	60	62.22	61

CAMCOG = Cambridge Cognitive Examination, MMSE = Minimental Status examination test; MOMSSE = Mattis Organic Mental Syndrome Screening Examination.

4. Discussion

Current results showed that there was no significant differences between the two groups as regard the age, gender or education. This was consistent with the findings of another study [21] which showed lack of relationship between glycemic control and either age or gender.

On the other hand, this was not consistent with the findings of another study [22] which demonstrated that poor glycemic control was least common among those aged ≥ 65 years (6.8%) and most common among adults aged 18 - 39 years. They explained the sub-optimal glycemic control observed among young people by the possible reflection of less interaction with the health system among young people. In the current study the insignificant association between age and DM control could be attributed to the insignificant age difference between both groups.

The absence of significant difference between both groups in education could be attributed to the insignificant association between education and follow up status.

In the current work, comparison of the duration of DM diagnosis between the two groups was not significant. This might be due to the difficulty of estimating DM duration, especially in older adults as patients usually have longer duration of DM. DM is frequently diagnosed after a long period of its occurrence. The international DM foundation overall estimates that, across all the surveys, approximately 50% of all people with DM were undiagnosed [23]. This implies that 50% of persons with DM are not diagnosed.

Regarding cognition, our study showed that there was no significant difference between the two groups as regard the age and education adjusted MMSE total score. On the other hand, other batteries, CAMCOG and MOMSSE which assess a wide range of mental abilities, for cognitive assessment showed significant difference between the 2 groups.

There was a significant difference between the two groups as regard the MOMSSE below average and aver-

age scores, as the below average score was more common in uncontrolled group, while the average score was more common in the controlled group.

These findings are supported by the findings of van Harten, *et al.* [24] who show a negative relation between HbA1C (chronic exposure to hyperglycemia) and cognition in Type 1 [25] and Type 2DM. Similarly Munshi, *et al.* [6] have demonstrated an inverse relationship between HbA1c and executive functioning and complex psychomotor performance in patients with Type 2DM.

Furthermore, our study showed that there was a highly significant difference between the two groups as regard CAMCOG score which was significantly higher in the controlled group. This could be attributed to the fact that CAMCOG contains more items on memory, language, and construction and allows a more differentiated judgment about these functions than the MMSE.

Our study revealed that CAMCOG had better sensitivity and MOMSSE had better specificity for the prediction of uncontrolled DM.

The better specificity of MOMSSE could be linked to its testing of certain cognitive functions that could be affected by DM, as most of its items namely memory, executive functions (digit span backward in the attention item using working memory, verbal abstraction item), language, visuospatial (construction skills), insight into illness, which is affected by memory, as verbal memory had an effect on total insight and all dimensions of insight, [26] and general fund of information which is also related to memory [13]. These functions are known to be affected in DM as reported by different studies. For instance, a study found ineffective top-down control of the prefrontal cortex which is involved in executive functions in Type 1DM. Furthermore, inter-network connections between the strategic/executive control system (in prefrontal cortex) and systems subserving other cortical functions including language were also less integrated in Type 1DM patients than in healthy individuals [27]. Moreover, another study suggests that the hippocampus and parahippocampal gyrus may be particularly vulnerable to the deleterious effects of Type 2DM. The parahippocampal gyrus in particular may play a crucial role in the memory impairments frequently reported in Type 2DM [28].

On the other hand, CAMCOG was more sensitive to assess cognitive functions as it includes more items that assess wider variety of cognitive functions not included in MOMSSE as praxis involved in parietal region of the brain [29], tactile perception also involved in the parietal region [30], visual perception involved in occipital region [31]. Whereas DM is known to affect areas in the brain that involve some cognitive functions as reported by different studies [27] [28].

As regards Depression, our study found a significant difference between the two groups as regard the presence of depression. This was not consistent with the finding of Munshi, *et al.* [6] who reported that glycemic control was not associated with the presence of depression as assessed by the GDS. This can be due to the smaller size of sample used in their study and also that it was conducted at a tertiary care specialty setting. Although the severity of depression was not disclosed by authors, they considered that the collected patients tend to be highly motivated, educated, and have excellent support systems. Therefore we might suggest less severe depression in their population, as it is known that depression is negatively correlated with education along with their excellent support system [32].

On the other hand, our study was consistent with finding of Lustman & Clouse [33] who reported that Depression has been shown to have a significant positive association with HbA1c.

In the current study, there was no significant difference between the two groups as regard the anxiety diagnostic criteria. This was not consistent with the findings of Masmoudi, *et al.* [34] who found that subjects with uncontrolled DM had a higher average anxiety score than those having a good glycemic control. This might be due to the difference in the tests as we used DSM-IV criteria [17] and they used the Hospital Anxiety and Depression Scale (HADS), which is a psychometric scale used as a screening tool. Masmoudi *et al.* [34] considered that using a screening psychometric scale, rather than a structured interview, to evaluate anxiety is a limitation to their study. This might basically pick up cases with severe anxiety.

On the other hand, our findings were supported by the findings of Gois *et al.* [35] who found that anxiety symptoms and vulnerability to stress on their own were not predictive of glycemic control.

As regards functional status, in the current study ADL showed a highly significant difference between the two groups where the controlled group was more independent than the uncontrolled group. Similarly, the IADL showed significant difference between the two groups as the controlled group was more independent than the uncontrolled group.

This can be supported by Kalyani *et al.* [36] who found that uncontrolled HbA1C and comorbidities ac-

counted for up to 85% of the excess risk of disability, largely due to cardiovascular disease and obesity, whereas poor glycemic control alone only accounted for up to 10% of the excess risk of disability. Also, other studies reported a 2 - 3 times greater risk of difficulty in performing ADL, and IADL tasks among older adults with DM compared with adults without DM [37] [38]. Also, Waidyatilaka *et al.* [39] found that physical activity was negatively correlated with HbA1c and sedentary behavior was positively correlated with HbA1c levels.

Regarding ability of self application of treatment; our study showed a significant difference between the two groups as the majority of the uncontrolled were those who received treatment by caregiver rather than by self. This was convenient with our findings that the uncontrolled group was more dependent in ADL & IADL. This is consistent indirectly with the ideas discussing the association between dependency and poor glycemic control [36].

Also, there was a significant difference between the two groups as regard the follow up status, where those who used to follow up their blood glucose were found to be more in the controlled group.

Our findings was not consistent with the findings of Harris [39] who found that follow-up frequency by self screening was not related to glycemic control, as measured by HbA1c level. This difference could be attributed to that subjects of our study were following up at outpatient clinic, so they received useful medical advice.

Meanwhile, our findings were supported by a study of Deiss *et al.* [40] that demonstrated that real-time continuous glucose monitoring (a method to measure glucose levels in real-time throughout the day and night. It also sends the information to a monitoring and display device to the patient and clinicians to make proper intervention) gradually improved glycemic control over 3 months, resulting in a reduction in HbA1c by at least 1% in half of the patients and at least 2% in one-quarter.

In the current study, there was no significant difference between the two groups as regard the type of treatment used. This was supported by the findings of the United Kingdom prospective DM study, in which subjects were randomized to four groups: insulin, sulfonylurea, metformin, or continued diet therapy. Only 50 percent of the patients in any group had HbA1C levels of less than 7% after three years [41].

In addition, the current study showed that there was a highly significant difference between the two groups as regard the levels of the TC, LDL and TG. However, there was no significant difference between the two groups as regard the HDL. This was supported by Petitti *et al.* [42] who found that there were significant trends of higher levels of TC, LDL, TG, (but not HDL) with higher HbA1c concentrations for both DM types.

5. Conclusion

Cognitive impairment was associated with poor glycemic control. Impairment in attention and abstraction, related to executive function, functions were found to be associated with poor glycemic control. These functions may be more needed in self management of DM and hence affected glycemic control. Also, depression was associated with poor glycemic control but anxiety was not. Poor functional state, application of treatment by other person and poor follow up of glucose were all associated with poor glycemic control.

6. Recommendation

Causal relation between poor glycemic control and both cognition and depression is suggested to be studied in a follow up study.

Funding

This paper was partially funded by Ain Shams University, there were no sponsors.

Acknowledgements

The authors would like to thank Ain Shams University, faculty of medicine for the partial funding of this paper.

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List of Abbreviations

ADL: Activities of Daily Living
AUC: Area under the Curve
CAMCOG: Cambridge Cognitive Examination
DM: Diabetes Mellitus
DSM-IV TR: Diagnostic & Statistical Manual 4th Edition Text Revision
FPG: Fasting Plasma Glucose
GDS: Geriatric Depression Scale
Hb-A1C: Hemoglobin A1c = Glycated Hemoglobin
HDL: High Density Lipoprotein
IADL: Instrumental Activities of Daily Living
LDL: Low Density Lipoprotein
MMSE: Mini Mental-State Examination
MOMSSE: Mattis Organic Mental Syndrome Screening Examination
P Value: Probability
PPG: Postprandial Plasma Glucose
ROC: Receiver Operating Characteristic
SD: Standard Deviation
SPSS: Statistical Package for Social Science
TC: Total Cholesterol
TG: Triglycerides