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Cognitive performance of older adults in a specialized diabetes clinic

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Abstract

Background: Diabetes mellitus is a risk factor for cognitive changes, but assessment for cognitive disorders in this population is performed infrequently. The present study examined the frequency of cognitive disorders and patterns of deficit in patients enrolled in a specialized clinic for diabetes.

Methods: A cross-sectional study was conducted to assess cognition in Mount Sinai Diabetes Center patients. Thirty eligible subjects aged ≥50 years were assessed and compared with non-diabetic cognitively normal control subjects, as well as non-diabetic subjects with mild cognitive impairment (MCI). The main outcome(s) and measure(s) were obtained through cognitive assessment and diagnosis using the Alzheimer's Disease Centers' uniform data set.

Results: Forty percent of subjects were newly diagnosed with a cognitive disorder: 10% were diagnosed with dementia and 30% with MCI. Diabetic subjects performed worse on the Mini-Mental State Examination (27.2 vs 28.4; $P = 0.0132$), list generation (9.5 vs 12.2; $P = 0.0190$), Trail Making Test, Parts A (70.1 vs 43.0; $P < 0.0001$) and B (197.2 vs 123.6; $P < 0.0001$), and the Digit Symbol test (12.7 vs 40.1; $P < 0.0001$) than cognitively normal individuals. Compared with subjects with MCI (amnestic type), diabetic subjects performed better on tasks of immediate and delayed recall (11.2 vs 7.3 [$P = 0.0048$] and 8.4 vs. 4.1 [$P = 0.0003$], respectively).

Conclusions: Undiagnosed cognitive disorders are common and underappreciated in patients being treated in a specialized diabetes clinic. It may be important to make cognitive assessment a standard part of patient assessments.

Keywords

Alzheimer's disease; cognition; dementia; diabetes-related complications; type 2 diabetes mellitus

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Introduction

According to the American Diabetes Association (ADA), more than 26% of Americans over the age of 65 years are affected by diabetes.[1] Worldwide, it is estimated that 387 million people are living with diabetes and 46.3% of these go undiagnosed.[2] Among many other complications, diabetes is a known risk factor for the development of cognitive decline and dementia.[3–5] Emerging data show a complex relationship between diabetes and cognitive dysfunction, with each condition posing higher risk for the development of the other. Prediabetic markers of insulin resistance, such as HbA1c and obesity, also confer risk for dementia.[6–8] A hyperinsulinemic state, typical of insulin resistance, in itself doubled the risk of Alzheimer's disease (AD).[9] In fact, it has been shown that insulin resistance and peripheral hyperinsulinemia affect processing of amyloid beta (Aβ; a peptide that is crucial in the formation of amyloid plaques found in the brains of those with AD) and inflammatory changes, potentially promoting memory impairment and AD.

However, most neuropathological studies point away from viewing diabetes as a risk factor for AD neuropathology. For example, Beeri et al.[10] found that diabetics have fewer neuritic plaques and neurofibrillary tangles (NFTs) in the cerebral cortex and fewer plaques in the hippocampus on autopsy compared with non-diabetics.

Imaging studies have also demonstrated a structural correlation between diabetes and brain changes. Diabetes has been associated with mild brain atrophy and greater likelihood of cerebral infarcts, particularly subcortical lacunar infarcts.[11,12] However, whether diabetes-associated atrophy is related to direct neurodegenerative processes or via vascular mechanisms is not yet known. Despite these pathological connections, cognitive outcomes in clinical trials have been overall disappointing. Multiple randomized trials have so far shown no long-term benefit from intensive glucose control on cognition.[13–15]

The presence of cognitive impairment can interfere with many aspects of a patient's medical care. This is especially the case when caring for patients with diabetes, because treating this condition encompasses complex medication regimens and monitoring of glucose levels, as well as complicated dietary changes and lifestyle modifications. In addition, rapidly changing treatment plans, many of them carrying the potential for dangerous adverse effects, further complicate the treatment of patients with cognitive deficits.

Most patients with diabetes mellitus are inadequately assessed for cognitive decline and thus may have undiagnosed cognitive changes or dementia that may be interfering with their diabetes care. With an increasing percentage of America's elderly population being affected by both diabetes and AD, the evidence of a possible relationship between both illnesses may have significant implications for the prevention and treatment of AD.[16–19]

Despite the abundance of data on pathogenic ties between diabetes mellitus and cognition, the epidemiology and demographic determinants of cognitive impairment or dementia within specific clinical populations being treated for diabetes have not been fully studied. Given the potential link between these conditions, more data on the prevalence and pattern of cognitive impairment in this population are needed.

Methods

We conducted a cross-sectional study assessing the cognition of patients presenting to the Mount Sinai Diabetes Center. Eligible subjects were identified by staff endocrinologists and asked to undergo a brief memory screening as part of their visit. Inclusion criteria stipulated that patients be aged ≥50 years, of either sex, fluent in English or Spanish, and with at least 4 years of education. Patients who had known or active psychiatric disorders, such as schizophrenia, mental retardation, major depression, or substance-related disorders, were excluded. Patients with known neurological disorders associated with cognitive deficits, such as stroke, Parkinson's disease or Huntington's disease, were also excluded.

First, the Folstein Mini-Mental State Examination (MMSE) was administered to eligible subjects. After reviewing the results of the screen with patients and their endocrinologists in the clinical setting, all subjects were then invited to the Mount Sinai Alzheimer's Disease Research Center (ADRC) for a full memory evaluation, regardless of score. The Mount Sinai ADRC is a comprehensive research facility and clinical program dedicated to the study and treatment of both normal aging and AD. Consent was obtained under the existing ADRC consent document, with appropriate institutional review board approval.

Evaluation included a thorough medical and psychiatric history, physical examination, and collection of the uniform data set (UDS). The UDS, designed by The Alzheimer's Disease Centers (ADC) program of the National Institute on Aging (NIA), is a systematic and standardized method of assessing patients and cognitively intact individuals for neurodegenerative diseases, in particular AD. The UDS includes data on demographics, medical history, family history of cognitive impairment and dementia, current medications, and neuropsychological testing. The neuropsychological assessment provides data on attention, processing speed, executive function, episodic memory, and language. All testing was done in the subject's primary language. For example, testing was done in Spanish by Spanish-speaking testers for Spanish speakers.

Table 1 presents the cognitive tests administered in the UDS battery, along with domains tested and score range. Attention refers to selectively focused concentration on one aspect of the environment while ignoring other extraneous stimuli. Executive function describes a collection of brain processes that allow an individual to plan, organize, think abstractly, select relevant information, and initiate or inhibit activity. Executive function is dependent on speed of processing, allowing for greater efficiency of these higher-order cognitive processes. In addition to the UDS, data were collected on subjects' most recent HbA1c levels (within 3 months of neuropsychological evaluation) and self-reported diabetic microvascular complications to assess for correlation with cognitive performance.

Evaluations resulted in a specific diagnosis of the patient's cognitive status at ADRC consensus conferences, which were attended by a physician and a neuropsychologist with expertise in memory disorders. The purpose of these meetings was to examine and synthesize the clinical history, relevant laboratory and radiographic data, and psychometric testing to arrive at diagnoses based upon research criteria.

Consensus conferences divide individuals into three broad groups based on their clinical, radiological, and neuropsychological data: normal cognition, dementia, and mild cognitive impairment (MCI). Normal cognition is defined as the absence of MCI, dementia, or other neurological condition resulting in cognitive impairment. Mild cognitive impairment is defined as those who do not have normal cognition, but do not meet clinical criteria for dementia. Essentially, these are subjects whose cognition is not normal for age but whose functional abilities remain intact. Within this larger category, subjects are given a specific diagnosis depending on their particular cognitive profile. These diagnoses include amnestic MCI (memory impairment with or without deficits in other cognitive domains) and non-amnestic MCI (deficits in cognitive domain[s] other than memory). For subjects who have dementia, diagnosis is made regarding the specific etiology of the dementia. These diagnoses include probable or possible AD, dementia with Lewy bodies, probable or possible vascular dementia, alcohol-related dementia, frontotemporal dementia, or primary progressive dementia. For individuals who are felt not to be normal controls, but are not felt to have MCI or dementia, consensus clinicians can choose the diagnosis “impaired, not MCI”. This category may include subjects whose deficits are felt to be secondary to low education, medical or psychiatric conditions such as head trauma or learning disorders, and are not expected to progress.

In all, 101 patients were approached in the diabetes clinic after referral by the endocrinologist or nurse. They were all offered clinical screening with MMSE and information about participating in the study at that time. Of these 101 patients, 19 (18.81%) refused any participation at the time they were approached in clinic; 17 (16.83%) expressed interest in participating, were offered MMSE testing in the clinic, but later refused to participate for lack of interest; and 14 (13.86%) expressed continued interest in participating but were lost to follow-up for various reasons (e.g. missing multiple appointments, no telephone connection). Overall, 21 individuals (20.79%) did not meet the inclusion or exclusion criteria for participation, either at initial contact in the diabetes clinic or upon further review at their scheduled evaluation visit. Efforts were made to perform MMSE upon meeting patients in the diabetes clinic, but many were unable to complete these initial clinical exams due to other time constraints, such as medical appointments or child care responsibilities. Of the 101 patients in total who were approached, 24 completed the MMSE only and another 30 (29.70%) consented and completed full evaluations. Altogether, 101 individuals were approached, 21 were excluded, and 30 completed the study.

The comparison groups were selected from the Mount Sinai ADRC UDS, which consisted of 750 subjects as of 22 July 2010. The normal control group ($n = 189$) was selected as all subjects who did not have a history of diabetes and had a normal cognitive diagnosis at baseline. The amnestic MCI (aMCI) group ($n = 98$) was selected as all subjects within the data set who did not have a history of diabetes and had a diagnosis of aMCI at baseline.

Statistical analysis

Demographic data were compared between diabetic patients, cognitively normal patients, and patients with aMCI (both without diabetes) using χ^2 tests and two-sample *t*-tests. Two-sample *t*-tests were further used to examine the significance of differences in

neuropsychological scores between diabetics and normal controls and between diabetics and aMCI. In order to investigate whether such differences still exist after adjusting for demographic variables, multiple regression models were fitted. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Table 2 summarizes the demographic characteristics found in our cohort with diabetes and in comparison groups with normal cognition and aMCI. In all, 30 subjects from the diabetes clinic were included in the analysis. The diabetic group was significantly younger than non-diabetic patients with normal cognition and aMCI (mean age 64.4 vs 78.1 and 79.2 years, respectively; $P < 0.0001$). The diabetic subjects were significantly less well educated (mean 9.6 vs 14.9 and 14.0 years of education, respectively; $P < 0.0001$), predominantly female (80%) and Hispanic (66.7% vs 7.4% and 12.2%, respectively; $P < 0.0001$). Subjects recruited from the diabetes clinic were also less likely to speak English as their primary language than those with normal cognition and aMCI (63.3% vs 90.0% and 88.8%, respectively; $P < 0.01$).

HbA1c levels estimate blood glucose levels over time. In our cohort, HbA1c levels ranged from 5.80% to 14.30% with a mean (±SD) of 8.2 ± 2.0%. Despite being managed in a specialized clinic for diabetes, 69.97% of subjects had HbA1c levels over 7.0%, indicating inadequate glycemic control. With regard to subjects' cognition, a full 40% of the cohort was found to have cognitive disorders, with 10% receiving a diagnosis of dementia (two subjects were diagnosed with probable AD and one with vascular dementia) and 30% receiving a diagnosis of MCI (six with the amnestic type, three with the non-amnestic type). When the MMSE scores of those fully evaluated were compared with those who only completed the MMSE for the clinical screen, there was no significant difference.

Cognitive test scores for each group are given in Table 3. *P*-values are reported for comparisons of age-and education-adjusted performance. Diabetic subjects performed significantly worse on the MMSE, vegetable list generation, Trail Making Test Part A, Trail Making Test Part B, and the Digit Symbol test than cognitively normal individuals (Table 3). When diabetic subjects were compared with aMCI subjects, diabetic individuals performed significantly better on memory tasks, demonstrating superior scores on immediate and delayed recall (Table 3). Otherwise, there were no significant differences in scores between diabetic subjects and those with aMCI, with the exception of the Digit Symbol test, where individuals with diabetes again demonstrated poorer performance (Table 3).

Discussion

In a cohort of subjects being seen in a specialized clinic for the treatment of diabetes mellitus, we found a full 40% with a diagnosable condition of cognitive impairment. These individuals performed significantly worse on cognitive testing than an age- and education-adjusted group of cognitively normal, non-diabetic elders. These findings are consistent with many prior studies that have found that diabetes is associated with cognitive decline.[20] However, diabetic subjects in the present study had a distinct pattern of cognitive deficits:

they did significantly worse on examinations that measure cognitive processes such as attention, speed of processing, and executive function. This differential pattern of decline is consonant with one longitudinal study that found that diabetes was specifically related to a decline in processing speed.[21]

Perhaps most relevant is how the deficits we found may affect a patient's diabetes care. All the 101 patients approached in the diabetes clinic were encouraged by their primary physicians to participate in a clinical screen of their memory. Despite enthusiasm from staff and their physicians, a striking number of patients were not interested or ultimately unable to participate. Fifty-seven patients refused any further participation outright, whereas 14 of the 44 who were eligible and interested in participating (many of them with cognitive complaints) did not complete the cognitive evaluations. Frequently, subjects missed appointments due to lack of scheduling and planning for visits, later requesting multiple new appointments that were also often missed. The problems these patients had in getting to their appointments are perhaps not surprising given the performance of their peers on tests of executive function. It seems particularly important to consider the cognitive status of these patients given the relative complexity of adhering to a diabetic diet, checking blood glucose levels, attending frequent clinic visits, and complying with diabetes medication regimens. Indeed, the HbA1c of the diabetic cohort in the present study indicate difficulties in this regard. Moreover, the comparability in MMSE scores between those who did and did not participate in the full evaluations may indicate that these deficits are widespread, and patients either ignore or are unaware of these problems.

In the present study of 30 subjects, we found that the cognitive profile in patients with diabetes is different from those with aMCI, who are at high risk for developing AD. If diabetes is suspected to be a risk factor for AD, one may predict that diabetics' performance in cognitive testing would be similar to that of patients with aMCI. However, our diabetic patients performed better in all memory tests than subjects with aMCI. Given that our testing battery was designed to specifically evaluate AD, which typically occurs in older subjects, it may have been insensitive to memory problems present in younger subjects. However, it did capture cognitive deficits in a wide range of non-memory areas that are often not (or only mildly) affected in AD. This observation supports the notion of a specific profile of cognitive impairment associated with diabetes that is different from profiles of other neurodegenerative diseases. Conversely, it is possible that diabetic patients develop amnestic deficits, in addition to the non-amnestic deficits we observed, as their cognitive disorder progresses.

Recent studies suggest that medication such as intranasal insulin may have cognitive benefits in patients with early AD.[22] In addition, insulin use has even been associated with a reduction in AD pathology itself among patients with AD.[23] Perhaps treatment reduced pathology and clinical symptoms in our cohort of diabetic subjects, distinguishing them from subjects with aMCI.

The different profiles of cognitive deficits in diabetics and those with aMCI suggest separate pathways of disease. Because diabetics are at increased risk of small-vessel disease, which has been shown to impair prefrontal cortex processing tasks such as executive function and

attention, it is possible that the findings of the present study support a model of cognitive decline due to the association of diabetes with vascular disease. In the Canadian Health Study of Aging of over 5000 patients, the presence of diabetes was associated with vascular cognitive impairment and an increased risk of vascular dementia at the 5-year follow-up.[24] However, diabetes was not associated with AD. As such, both studies indicate that although diabetes is a risk factor for cognitive impairment, the risk is likely through vascular mechanisms rather than via Alzheimer's pathology.

There are many limitations to the present study. The sample size was small and largely minority. Subjects were recruited from a specialized diabetes clinic in which interest and concern about cognitive issues was not primary. This may have been responsible for the low levels of participation. Despite adjusting for demographic variables, the diabetic sample in the present study may not be representative of the larger population of diabetic individuals. Comorbid conditions such as hypertension and coronary artery disease, which are found more frequently in minority populations, may confound our findings. Moreover, our sample was 80% female. Given that recent data show that women with diabetes are more likely to have single-domain non-amnestic MCI,[25] these particular deficits may be overrepresented in the present sample. However, the nature of the deficit and the frequency with which it has been identified supports the likelihood that it is both a serious and common problem.

In conclusion, the findings of the present study demonstrate a high level of cognitive deficits in a sample of diabetic patients being treated in a specialty diabetes clinic. The deficits observed were primarily non-amnestic in nature, with the domains of attention and executive function significantly affected in diabetic subjects. Despite these findings and their implications for management, diabetic patients' cognitive problems remain relatively underappreciated by clinicians and patients. The data suggest that it is critically important to study the cognitive trajectory of these individuals longitudinally to better understand the relationship between diabetes and dementia. In the short term, it would be clinically useful for clinicians to build in baseline and ongoing cognitive assessment of their patients, in addition to standard diabetes care.

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Highlights

- Diabetes is associated with significant cognitive deficits that often go undiagnosed. However, the pattern of decline differs from the one seen in patients with mild cognitive impairment (amnestic type).
- This study adds to our knowledge about the connection between diabetes mellitus and cognition, and the particular pattern of cognitive deficit seen in diabetics.

Table 1

Description of cognitive tests

Test or measure	Domain or function	Maximum scores
MMSE	Dementia severity/global cognitive screen	Total MMSE: 30
		Total orientation items: 10
Digit Span Forward (WMS-R)	Attention	Longest sequence: 9
		Total correct trials: 14
Digit Span Backward (WMS-R)	Attention; also working memory	Longest sequence: 8
		Total correct trials: 12
Digit Symbol (WAIS-R)	Processing speed	Total no. items completed in 90 s: 99
Part A, Trail Making Test	Processing speed	Total time: 150 s
Part B, Trail Making Test	Executive function	Total time: 300 s
Logical Memory, Story A (WMS-R)	Memory	
	Immediate Recall	Total items recalled: 25
	Delayed Recall	Total items recalled: 25
Animal List Generation	Language: verbal fluency	Total items in 1 min
Vegetable List Generation	Language: verbal fluency	Total items in 1 min
Boston Naming Test (30 odd items)	Language: naming	Total correct: 30

MMSE, Mini-Mental State Examination; WMS-R, Wechsler Memory Scale – Revised; WAIS-R, Wechsler Adult Intelligence Scale – Revised.

Table 2

Participant characteristics

				P-value	
	Diabetic (*n* = 30)	**Normal (*n* = 189)**	**aMCI (*n* = 98)**	**Diabetic vs normal**	**Diabetic vs aMCI**
Age (years)	64.4 ± 7.4	78.1 ± 8.9	79.2 ± 8.8	<0.0001	<0.0001
Education (years)	9.6 ± 3.2	14.9 ± 3.3	14.0 ± 3.7	<0.0001	<0.0001
Sex				0.0004	<0.0001
Male	6 (20.0)	104 (55.0)	72 (73.5)		
Female	24 (80.0)	85 (45.0)	26 (26.5)		
Language				<0.0001	0.0012
English	19 (63.3)	170 (90.0)	87 (88.8)		
Non-English	11 (36.7)	19 (10.1)	11 (11.2)		
Ethnicity				<0.0001*	<0.0001*
White	1 (3.3)	149 (78.8)	68 (69.4)		
Black	7 (23.3)	20 (10.6)	17 (17.4)		
Hispanic	20 (66.7)	14 (7.4)	12 (12.2)		
Other	2 (6.7)	6 (3.2)	1 (1.0)		
Cognitive diagnosis					
Normal control	15 (50)				
MCI (amnestic)	6 (20)				
MCI (non-amnestic)	3 (10)				
Alzheimer’s disease	2 (6.7)				
VaD	1 (3.3)				
impaired, not MCI	3 (10)				
HbA1c (%)	8.2 ± 2.0				
Microvascular complications					
Retinopathy	12 (40.0)				
Neuropathy	11 (36.67)				
Nephropathy	6 (20.0)				

Data are given as the mean ± SD or as *n* (%), as appropriate.

**P*-value is not reliable because some cell numbers are <5. MCI, mild cognitive impairment; aMCI, amnestic MCI; VaD, vascular dementia.

Table 3

Comparisons of adjusted mean scores on the different tests

Test	Diabetic	Normal	Diabetic vs normal	Diabetic	aMCI	Diabetic vs aMCI
MMSE	27.2	28.4	0.0132	26.8	26.1	0.3166
Immediate Recall	12.2	11.5	0.4829	11.2	7.3	0.0048
Delayed Recall	8.7	10.5	0.0968	8.4	4.1	0.0003
Digif	7.1	7.9	0.1815	7.3	7.3	0.9840
Digib	4.4	5.5	0.0594	4.0	5.1	0.0663
Animal List	13.6	16.7	0.0530	13.0	12.0	0.5229
Vegetable List	9.5	12.2	0.0190	9.6	9.2	0.6897
TMT A	70.1	43.0	<0.0001	73.4	58.4	0.0836
TMT B	197.2	123.6	<0.0001	210.6	185.6	0.3158
Digit Symbol	12.7	40.1	<0.0001	13.2	32.5	<0.0001
Boston Naming	22.1	23.8	0.0754	22.0	21.3	0.6703

aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; Digif, Digit Span Forward; Digib, Digit Span Backward; TMT A, Part A, Trail Making Test; TMT B, Part B, Trail Making Test.