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Cognition in Non-Demented Diabetic Older Adults

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Abstract

Evidence links diabetes mellitus to cognitive impairment and increased risk of Alzheimer's disease (AD) and suggests that insulin therapy improves cognition. With an increasing percentage of the US elderly population at high risk for diabetes and AD, the evidence of an association between diabetes and poor cognition in non-demented elderly may have implications for diagnosis, prevention and treatment of cognitive decline including AD.

In our study, we hypothesized that diabetic elders with normal cognition would demonstrate poorer cognitive outcomes than non-diabetic elders and that diabetic elders receiving diabetes treatment would demonstrate better outcomes than those not receiving treatment.

Data were evaluated from the National Alzheimer's Coordinating Center's Uniform Data Set (UDS). The UDS consists of clinical and neuropsychological assessments of a sample of elderly research subjects recruited from thirty-one Alzheimer's Disease Centers nationwide. The UDS provides a unique opportunity to study cognition in a nationally recruited sample with structured neuropsychological tests.

We examined the impact of diabetes and diabetes treatment on cognitive measures in 3421 elderly research subjects from 2005-2007 with normal cognition. We performed linear regression analyses to compare cognitive scores between diabetic subjects and non-diabetic subjects. Diabetic subjects had lower scores than non-diabetic subjects including attention, psychomotor function and executive function, but no differences in memory or semantic memory language. There was no association between diabetes treatment and cognitive scores.

These subtle but significant cognitive deficits in diabetic subjects compared to non-diabetic subjects may contribute to difficulty with compliance with complex diabetes medication regimens. A specific role of diabetes as a risk for cognitive impairment will require longitudinal study.

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Keywords

Diabetes; Cognition; Alzheimer's; Elderly

Introduction

Several studies link diabetes to cognitive impairment described as diminished mental flexibility, impaired learning, memory and slowed mental speed [1-5]. A number of studies have found that dementia, including vascular dementia and Alzheimer's disease (AD), is higher in individuals with diabetes mellitus than in those without diabetes [6, 7]. Some [1-3, 8-17] but not all [18]studies have suggested that diabetes increases the risk of AD. Furthermore, elevated insulin levels, characteristic of type 2 diabetes, have been found to increase beta amyloid levels and inflammation often associated with AD neuropathology and memory loss [2, 3, 17].

Diabetes, especially type 2 diabetes, and dementia are common diseases among the elderly. The Alzheimer's Association estimates that 13% of Americans over the age of 65 have AD [19], while the United States Centers for Disease Control (CDC) estimates that nearly 24% of Americans over the age of 60 have diabetes [20]. 90-95% of all diabetes cases in the United States is classified as type 2 diabetes [20]. The evidence of an association between diabetes and poor cognition in elderly with normal cognition may have implications for diagnosis, prevention and treatment of cognitive decline including AD. In fact, some data have suggested that treatments that target type 2 diabetes may have a beneficial impact on AD [1, 2, 6, 7, 12, 15, 18].

In the present study, we performed a retrospective analysis of the impact of diabetes on elderly research subjects with normal cognition who participated in a national study aimed to characterize cognition in an aging sample of normal and cognitively impaired individuals. The study, the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS), was developed by a clinical task force appointed by the National Institute of Aging and consists of clinical and neuropsychological assessments performed by 31 Alzheimer's Disease Centers (ADCs) nationwide [21, 22]. The UDS provides a unique opportunity to study a large research population from across the United States. Furthermore, the cognition of UDS research subjects is well-characterized with eleven neuropsychological tests assessing different aspects of cognition.

Based on the literature described above, we hypothesized that subjects who self-reported diabetes would demonstrate poorer cognitive status than subjects who did not report diabetes. We also examined the impact of diabetes medication treatment, including insulin and oral hypoglycemics, on cognitive performance among diabetic subjects. We hypothesized that treated diabetic subjects would demonstrate better cognitive performance than untreated diabetic subjects.

Methods

Data Source, Diagnostic Group and Diabetes

Data submitted to the UDS between 2005 and 2007 were extracted on October 23, 2007. Data included UDS clinical and demographic outcomes as captured in 18 written forms completed by ADC clinicians and research staff. Diagnosis was recorded on the UDS form D1 “Clinician Diagnosis--Cognitive Status and Dementia” which was completed by a single clinician or by a consensus of clinicians at each site.

Subjects were clinically cognitive normal older adults who volunteered at the ADCs. Each Center uses its own recruitment strategy. According to referral information in the UDS database, participants were referred by a relative or friend, by a clinician or from a clinic sample (geriatrics, memory clinics, and other medical specialties), by ADC solicitation, by non-ADC media appeal and from other or unknown sources [22]. For this study we included cases with a diagnosis of Normal Control (N=3421) which is defined as "having normal cognition (no Mild Cognitive Impairment, dementia, or other neurological condition resulting in cognitive impairment) ". Cases were defined as diabetic or non-diabetic based on the presence of diabetes as recorded in the UDS medical history.

Depression was determined from items in the Neuropsychiatric Inventory (NPI) which is completed by an interview of a surrogate informant of the subject. NPI Item 5 asks, "Does the pt act as if he is sad or in low spirits? Does he or she cry?" with possible responses of Yes or No. We assessed depression and control for it in our analysis because depression has been associated with both diabetes and cognitive decline [23, 24].

Clinical and Cognitive Outcomes, including Composite Scores

Cognitive status was assessed with Mini Mental Status Exam (MMSE) and ten neuropsychological measures assessing 6 cognitive domains (immediate and delayed verbal episodic memory, attention, semantic memory/language, psychomotor speed, and executive function). Immediate and delayed verbal episodic memory was assessed by tests Logical Memory IA and IIA, attention by Digit Span backward, semantic memory/language by Animals and Vegetables and Boston Naming, psychomotor speed by Digit symbol and Trail A, and executive function by Trail B.

A composite score was created to summarize the MMSE and all ten UDS neuropsychological measures. More specifically, we first normalized the eleven test scores by dividing by their maximum possible scores and then took the sum of the normalized scores. Note that, for Trail A and Trail B, we reversed their directions so that all normalized scores point to the same direction in which a higher score signifies a better cognition. Both the raw score and maximum value were evaluated in time units (seconds). This approach to creating a composite score has been used in other studies assessing cognitive decline [25].

Diabetes Treatment Group

Data for diabetes medications among diabetic subjects were extracted from UDS "Subject Medications Form". Diabetic subjects were categorized as "treated" diabetic subjects if insulin or any hypoglycemic medications including sulfonylureas, meglitinides, biguanides, thiazolidinediones, or alpha-glucosidase inhibitors were listed. Diabetic subjects with none of these medications indicated were categorized as "untreated," although lifestyle interventions were not recorded.

Data Analysis

Descriptive analyses of demographic and clinical variables in diabetic vs non diabetic subjects were conducted. Means (and standard deviation) or frequencies were calculated for the demographic variables of age, education, sex, race, and depression. Two-sample t-tests were used to compare age and education between diabetic subjects and non-diabetic subjects. χ^2 tests were used to compare the sex, race, and presence of depression between diabetic subjects and non-diabetic subjects. Linear regression models, with the cognitive status outcome variables as the dependent variable and group indicator (diabetic or non-diabetic) as independent variable (adjusting for demographic variables listed above) were used to assess the difference in outcomes between diabetic and non-diabetic subjects. Outcome differences between diabetic subjects and non-diabetic subjects were determined

to be significant if $p<0.05$. Not all subjects included in the analysis had a complete dataset and were missing some outcome variables. The cases with missing variables were excluded from the analysis of the composite score. Two-sample t-tests were used to compare the age, education, and MMSE scores between subjects with complete datasets and those with missing outcome variables. The small and non-significant difference in MMSE between the excluded cases and selected cases indicates that the exclusion of those cases with missing outcome variables did not give us a biased sample in terms of cognition. We have adjusted for the potential bias effects of age and education in the model by putting them as covariates.

To analyze the impact of diabetes treatment, means and standard deviation were calculated for composite scores for treated and untreated diabetic subjects. Linear regression analysis was performed to compare composite scores between treated and untreated diabetic subjects controlling for age, education, sex, race, handedness and presence of depression.

Results

Results showed that 9.2% (n = 316) of participants (n = 3421) had diabetes. The diabetic group was less educated ($p<0.001$), more likely to be male ($p=0.004$), more likely to be of a minority group ($p<0.001$), and to have depression ($p<0.001$) than the non-diabetic group (Table 1). 448 out of 3421 total cases had missing outcome data. Participants with missing outcome data, when compared with participants with complete outcome data, were significantly younger (mean age 73.7 years vs. 77.4 years, p=<0.001) and more educated (mean years of education 15.6 vs 14.9, $p=0.0001$), with no significant difference in MMSE scores (28.9 vs. 28.8, $p=0.15$).

The diabetic subjects performed significantly worse on tests of attention (digit span backward, $p=0.0164$ and digit span backward length, $p=0.0058$), semantic memory and language (animals category fluency, $p=0.0170$), psychomotor functioning and visuospatial function (Trail A, $p<0.001$ and WAIS-R digit symbol, $p=0.011$), and executive function (Trail B, $p<0.001$) (Table 2).

Our summary measure of cognitive functioning, the composite score, was lower in diabetic subjects than in non-diabetic subjects ($p= 0.01$). There were no significant differences in Logical Memory IA, Logical Memory IIA, Boston Naming and MMSE scores.

In this sample 67.7% (n = 214) of all diabetic subjects (n = 316) were treated with insulin and/or hypoglycemic medications although about one third were not. There were no significant differences in composite scores between treated (Mean=5.5, SD= 0.9) and untreated (Mean=5.1, SD=1.2) diabetic subjects (Difference=-0.4, $p=0.35$).

Discussion

Among this healthy population, the present study identified poorer cognitive outcomes in elderly subjects with diabetes than in those without. Subtle but significant deficits were found in many important areas of cognitive function, including memory, attention, psychomotor function and executive function. These findings are supported by other studies that found diminished cognitive performance in normal, Mild Cognitive Impairment and AD diabetic subjects [1, 2]. The functional impact of these cognitive deficits is not clear, but may exacerbate problems with planning and execution of normal activities and contribute to non-compliance with diabetes treatment regimens. Importantly, these subtle deficits are likely missed by patients and family members and clinically should be detected with sensitive neuropsychological assessment similar to that used in the UDS.

The association of diabetes and poorer cognition in diabetic subjects may suggest that diabetes is a risk factor for cognitive decline. While there may be an increased risk of dementia it is notable that memory performance in Logical Memory IA and IIA was not affected by the presence of diabetes. Similarly, a prior study has found that type 2 diabetic subjects with normal cognition have decreased processing speed and executive function, but no memory deficits, compared to non-diabetic subjects [8]. The pattern of poorer performance in attention and executive function is reminiscent of vascular dementia.

The majority of our subjects with diabetes were undergoing some type of diabetes treatment, including insulin and oral hypoglycemic therapy. We found no significant differences in composite score performance between treated and untreated diabetic subjects. Previous studies have reported diabetes medications have salubrious effects on cognition in non-diabetic memory impaired adults [2, 26, 27]and that anti-diabetic drugs, specifically insulin, were associated with less AD neuropathology in the postmortem brains of AD patients [27]. While small studies of some agents have yielded positive results [28], randomized multi-center clinical trials with one anti-diabetic agent yielded a benefit only in a subgroup analysis in memory impaired subjects and those with AD [26]. Our diabetic subjects, though performing poorer than non-diabetic subjects were only minimally impaired and perhaps ceiling effects mitigate the ability to see a benefit of anti-diabetic treatment.

However, our data on treated and untreated diabetic subjects was greatly limited. We do not know diabetes disease duration, fasting glucose, or hemoglobin A1C levels. It is possible that treated diabetic subjects in fact have poorer glucose control, longer disease duration and thus may be at greater risk of developing cognitive deficits than untreated diabetic subjects. Moreover, the UDS lacks data for other factors that could also confound the relationship between treatment and cognition, including socioeconomic status, treatment compliance, and co-morbidities. Thus, we could not truly assess whether “treated” diabetic subjects indeed had better glucose control than “untreated” diabetic subjects, who may have had milder disease or disease controlled by diet and exercise instead of medication.

Importantly, presence of diabetes is based on self report in a medical history and is without confirmatory laboratory results. This lack of laboratory data may result in diabetes underdiagnosis by as much as thirty percent [7]. The data set does not delineate between type 1 or type 2 diabetes. However, type 2 diabetes is more prevalent than type 1 diabetes in the elderly [7, 20] and it is thus likely that our diabetic sample reflects predominantly type 2 diabetes.

Moreover, the 9.24 % prevalence of diabetes among our subjects is markedly lower than the 23.8% prevalence the CDC estimates for Americans over age 60 [20], suggesting that the study population may not accurately reflect the rate of diabetes in a typical elderly American population. Along these lines, Morris *et al.* assert that UDS subjects, as part of a unique sample consenting to participate in a longitudinal study, are unlikely to be representative of the general US elderly population [21]. UDS subjects may be healthier than the general US elderly population, with lower rates of disease such as diabetes and cardiovascular disease, and thus more likely to volunteer for longitudinal study.

Another potential limitation is the possibility that common early life risk factors may underlie both poorer cognition and diabetes and the relationship may not be causal. The differences we found between diabetic and non-diabetic subjects may be due to cognitive ability differences that are independent of diabetes. However, we attempted to limit confounding by controlling for age, education, sex, ethnicity and depression. Aside from education, we have no data on early life risk factors or subjects' inherent cognitive ability; however the group was collected from tertiary medical centers and highly educated.

We do not have full characterization of cerebrovascular correlates such as neuroimaging. Such data would allow us to better determine if the cognitive deficits are associated with neurovascular burden.

In summary, this study provides evidence of an association between poorer cognitive performance and diabetes among non-demented individuals. Our findings along with many other studies that find diabetes associated with diminished cognition may encourage physicians treating diabetic subjects to regularly assess patients annually for cognitive decline [10].

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Table 1

Means and Standard Deviations (SD) of Demographic Characteristics across the Diabetic and Nondiabetic Subjects

	Non-diabetic Subjects		Diabetic Subjects			
Descriptives	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**Difference**	**P-value***
Age	3105	74.1 (10.4)	316	74.7 (8.8)	-0.5	0.392
Education	3069	15.6 (3.7)	315	14.7 (3.5)	0.9	<0.001†
		%		%		
% Male	3105	34.9	316	43.0	--	0.0041†
%Caucasian	3105	88.3	316	69.0	--	<0.001†
Presence of Depression	2772	12.1	287	23.7	--	<0.001†

*P-values for Age & Education are from 2 sample t tests. P-values for Sex, Race, and Presence of Depression are determined from χ^2 tests.

†= significant, $p<0.05$

Table 2

Means and Standard Error (SE) of Cognitive Outcomes across the Diabetic and Nondiabetic Subjects

		Nondiabetic Subjects		Diabetic Subjects			
Cognitive Measure	**Cognitive Domain [21, 22]**	**N**	**Mean (SE)**	**N**	**Mean (SE)**	**Difference (SE) §**	**P-value***
Mini Mental Status Exam	General Dementia Screen	3079	27.0 (0.03)	316	28.5 (0.12)	0.14 (0.09)	0.112
Logical Memory IA	Immediate Verbal Episodic Memory	2999	13.9 (0.07)	299	13.2 (0.23)	-0.13 (0.24)	0.602
Logical Memory IIA	Delayed Verbal Episodic Memory	3002	12.5 (0.08)	298	11.6 (0.26)	-0.09 (0.27)	0.745
Digit span backward	Attention	3035	6.9 (0.04)	306	6.2 (0.12)	0.32 (0.13)	0.016†
Digit span backward length	Attention	3035	5.0 (0.02)	306	4.6 (0.07)	0.21 (0.08)	0.005†
Animals	Semantic Memory/Language	3069	20.1 (0.10)	310	18.2 (0.28)	0.79 (0.33)	0.017†
Vegetables	Semantic Memory/Language	3011	14.5 (0.08)	307	13.5 (0.26)	0.39 (0.95)	0.136
Trail A	Psychomotor Speed	3028	35.0 (0.30)	306	43.0 (0.30)	-4.36 [0.95]	<0.001†
Trail B	Executive Function	3014	91.2 (0.93)	300	113.2 (0.92)	-9.72 [2.88]	<0.001†
WAIS-R Digit symbol	Psychomotor Speed	2786	46.7 (0.24)	275	41.3 (0.75)	1.80 (0.71)	0.011†
Boston Naming	Semantic Memory/Language	3004	27.1 (0.06)	306	26.1 (0.26)	0.10 (0.19)	0.592
Composite Score	N/A	2715	5.8 (0.03)	258	5.4 (0.09)	0.12 (0.05)	0.014†

*P-values for all cognitive measures are determined from linear regression analyses

†= significant, p<0.05

§Difference adjusted for demographics of age, education, gender, race, handedness, and presence of depression

‖A higher numerical score on this measure indicates diminished clinical status