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Diabetes, Glucose Control, and 9-Year Cognitive Decline Among Older Adults Without Dementia

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Objectives: To determine if prevalent and incident diabetes mellitus (DM) increase risk of cognitive decline and if, among elderly adults with DM, poor glucose control is related to worse cognitive performance.

Design: Prospective cohort study.

Setting: Health, Aging, and Body Composition Study at 2 community clinics.

Participants: A total of 3069 elderly adults (mean age, 74.2 years; 42% black; 52% female).

Main Outcome Measures: Participants completed the Modified Mini-Mental State Examination (3MS) and Digit Symbol Substitution Test (DSST) at baseline and selected intervals over 10 years. Diabetes mellitus status was determined at baseline and during follow-up visits. Glycosylated hemoglobin A_{1c} level was measured at years 1 (baseline), 4, 6, and 10 from fasting whole blood.

Results: At baseline, 717 participants (23.4%) had prevalent DM and 2352 (76.6%) were without DM, 159 of whom developed incident DM during follow-up. Participants with prevalent DM had lower baseline test scores than participants without DM (3MS: 88.8 vs 90.9; DSST: 32.5 vs 36.3, respectively; $t=6.09$; $P=.001$ for both tests). Results from mixed-effects models showed a similar pattern for 9-year decline (3MS: −6.0- vs −4.5-point decline; $t=2.66$; $P=.008$; DSST: −7.9- vs −5.7-point decline; $t=3.69$; $P=.001$, respectively). Participants with incident DM tended to have baseline and 9-year decline scores between the other 2 groups but were not statistically different from the group without DM. Multivariate adjustment for demographics and medical comorbidities produced similar results. Among participants with prevalent DM, glycosylated hemoglobin A_{1c} level was associated with lower average mean cognitive scores (3MS: $F=8.2$; P for overall $=.003$; DSST: $F=3.4$; P for overall $=.04$), even after multivariate adjustment.

Conclusion: Among well-functioning older adults, DM and poor glucose control among those with DM are associated with worse cognitive function and greater decline. This suggests that severity of DM may contribute to accelerated cognitive aging.

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In the United States, approximately 27% (10.9 million) of adults 65 years and older have diabetes mellitus (DM).[1] The risk of both DM and cognitive impairment increases with age. Findings from several studies suggest an association between DM and increased risk of cognitive impairment and dementia, including Alzheimer disease.[2-5] However, the association between DM and cognitive function in older adults continues to be debated, and less is known regarding incident DM in late life and cognitive function over time.

Many studies report a link between DM and decreased cognitive function, with a stronger association found in older (>60 years) adults compared with younger groups.[6-8] However, most studies investigating DM and cognitive function have either been case-control or prospective studies that focused on prevalent DM determined only at baseline.[2,5] Little is known about cognitive function in older adults with newly diagnosed DM, limiting our understanding of the association between emergent DM and cognitive performance. In addition, poor glucose control, measured by glycosylated hemoglobin A_{1C} (HbA_{1c}) level, has emerged as a possible risk factor for cognitive decline among elderly adults with DM; results, however, have been inconsistent.[9-14]

We sought to evaluate the association between prevalent and incident DM and cognitive function at baseline and over time in a diverse group of well-function-

ing older adults. Our secondary aim was to determine if glycemic control, as measured by HbA_{1c} level, among those with DM is associated with cognitive function. Our hypothesis was that participants with prevalent DM would have worse cognitive function over 9 years compared with those without DM and that participants with incident DM would have a decline in cognitive function intermediate between those with prevalent DM and those remaining free of DM. Among those with prevalent DM, we hypothesized that higher HbA_{1c} level would correspond to lower cognitive scores.

METHODS

STUDY POPULATION

Participants were enrolled in the Health, Aging, and Body Composition (Health ABC) Study, a prospective cohort study beginning in 1997 of 3075 community-dwelling white and black older adults then aged 70 to 79 years living in Memphis, Tennessee, or Pittsburgh, Pennsylvania. Participants were recruited from a random sample of white Medicare-eligible elderly adults within the designated zip codes and all age- and function-eligible black adults. Exclusion criteria included reported difficulties performing activities of daily living, walking a quarter of a mile, or climbing 10 steps without resting. Participants also had to be free of life-threatening cancers and planning to remain within the study area for at least 3 years.

This study was approved by the institutional review boards of the University of Pittsburgh and the University of Tennessee, Memphis, and that of the coordinating center, the University of California, San Francisco. All participants signed an informed written consent, approved by the institutional review boards at the clinical sites.

MEASUREMENTS

Prevalent DM was defined at baseline by self-report, use of hypoglycemic medication, a fasting glucose level of 126 mg/dL or more (to convert to millimoles per liter, multiply by 0.0555), or a 2-hour glucose tolerance test level more than 200 mg/dL, in accordance with the American Diabetes Association criteria in place near the start of the Health ABC study (American Diabetes Association 2002). Diabetes mellitus status was assessed at each follow-up visit by self-reported DM status or hypoglycemic medication use or by elevated fasting glucose level taken at years 2, 4, and 6. Those who developed DM during follow-up were defined as having incident DM.

The HbA_{1c} level was measured at years 1 (baseline), 4, 6, and 10 from fasting whole blood using fully automated analyzers that utilize nonporous ion-exchange high-performance liquid chromatography for separation of HbA_{1c}. The HbA_{1c} level was analyzed by approximate tertile as low (<7%), mid (7%-8%), and high (≥8%).

The Modified Mini-Mental State Examination (3MS) was administered at the baseline visit (year 1) and repeated at the year 3, 5, 8, and 10 follow-up visits. The 3MS is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory.[15] Scores range from 0 to 100 points, with lower scores indicating poorer performance. The Digit Symbol Substitution Test (DSST), administered in years 1, 5, 8, and 10, measures attention, psychomotor speed, and executive function.[16] The DSST score was calculated as the total number of test items correctly coded in 90 seconds, with a maximum (best) score possible of 90.

COVARIATES

Possible covariates included the baseline self-reported age, race, sex, level of education (categorized as less than high school, some high school, and high school or more education), and number of alcoholic drinks per day (categorized as less than 1 vs 1 or more drinks per day). Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression Scale.[17] Body mass index was calculated from direct height and weight measurements at baseline as weight in kilograms divided by height in meters squared. Hypertension was determined using self-report, medication use, and clinical measurements taken at the baseline examination. Stroke and myocardial infarction were based on self-report, clinic data, and medication use. Apolipoprotein E genotype was determined by the 5′-nuclease assay[18] in the Human Genetics laboratory at the University of Pittsburgh and participants were coded as ε4 carriers or noncarriers.

STATISTICAL ANALYSES

We first performed bivariate analyses to test for associations between DM group and baseline characteristics. We used χ^2 analysis for categorical variables and the F test for continuous variables.

We used mixed-effects linear regression models to determine the association between DM group and baseline test scores as well as change in scores over 9 years. The mixed-effects linear regression models estimated the change in cognitive scores over time allowing person-specific differences in the cognitive score at baseline and rate of cognitive decline. Incident DM was treated as a time-varying covariate, categorized according to DM determined during any of the follow-up visits. We then created a multivariate mixed-effects model adjusting for characteristics (time-dependent when possible) that significantly differed across DM group at baseline ($P < .05$) (**Table 1**) or that have been previously shown to be associated with cognitive function.

We next examined the association between HbA_{1c} level and cognitive test scores among participants with prevalent DM using unadjusted and adjusted mixed-effects linear regression models, similar to those used to test for associations between DM group and cognitive scores. Glycosylated hemoglobin A_{1c} status was treated as a time-varying covariate, updated with values obtained during the follow-up visit proximal to cognitive testing. Since HbA_{1c} level was analyzed using slightly different assays in the Health ABC study during separate years and the interaction between time and HbA_{1c} level was not significant, we assessed cognitive score at mean time of follow-up for HbA_{1c} values among those with prevalent DM.

All analyses were conducted using SAS statistical software, version 9.2 (SAS Institute Inc) and were 2-tailed, with the statistical significance level set at $P < .05$.

RESULTS

Of the 3069 participants in our study, 717 (23.4%) had prevalent DM and 159 (5.2%) developed DM over follow-up. The mean (SD) age of participants at baseline was 74.2 (2.9) years. Forty-two percent were black and 52% were female. Prevalent DM was associated with black race, being male, and having less than a high school education, a history of myocardial infarction or hypertension, and a higher body mass index (Table 1).

At baseline, persons with prevalent DM had lower unadjusted 3MS and DSST scores compared with those without DM ($t = 6.09$; $P = .001$ for both tests) (**Table 2**). Ad-

Table 1. Baseline Characteristics of the 3069 Participants by DM Status

Baseline Characteristic	No. (%) Non-DM (n = 2193)	Incident DM (n = 159)	Prevalent DM (n = 717)	*P* Value
Age, y, mean (SD)	74.1 (2.9)	73.7 (3.1)	74.2 (2.8)	.18
Black	828 (37.7)	75 (47.2)	374 (52.2)	<.001
Female	1180 (53.8)	78 (49.1)	326 (45.5)	<.001
Education				<.001
<High school	501 (22.9)	38 (23.9)	231 (32.4)	
High school	710 (32.5)	53 (33.5)	236 (33.3)	
Current smoker	241 (11)	15 (8.7)	62 (9.4)	.19
Alcohol use, ≥1 drink/d	172 (7.9)	13 (8.2)	42 (5.9)	.19
Stroke	160 (7.4)	17 (10.8)	69 (9.8)	.06
Myocardial infarction	228 (10.4)	24 (15.2)	105 (14.6)	<.001
Hypertension	1244 (56.7)	115 (72.3)	510 (71.1)	<.001
Body mass index, mean (SD)[a]	26.7 (4.6)	29.6 (4.9)	28.9 (4.9)	<.001
Depression score ≥16	88 (4.0)	7 (4.4)	26 (3.6)	.86
Apolipoprotein E ε4 carrier	596 (28.7)	49 (32.9)	191 (28.2)	.51

Abbreviation: DM, diabetes mellitus.
[a]Calculated as weight in kilograms divided by height in meters squared.

Table 2. Unadjusted Cognitive Test Scores by DM Status

	Mean (SE) Cognitive Test Score Non-DM (n = 2193)	Incident DM (n = 159)	Prevalent DM (n = 717)
Modified Mini-Mental State Examination			
Baseline	90.9 (0.2)	90.2 (0.5)	88.8 (0.3)[a]
9-y Change score	–4.5 (0.3)	–5.8 (1.4)	–6.0 (0.5)[a]
Digit Symbol Substitution Test			
Baseline	36.3 (0.3)	35.3 (0.7)	32.5 (0.5)[a]
9-y Change score	–5.7 (0.3)	–4.4 (1.8)	–7.9 (0.5)[a]

Abbreviation: DM, diabetes mellitus.
[a]*P* value < .05 compared with participants without DM.

justing for age, race, sex, and education produced similar results. Compared with those without DM, participants with prevalent DM had slightly lower mean 3MS baseline scores (89.7 vs 90.5; $t = 2.5$; $P = .01$) and DSST scores (34.3 vs 35.5; $t = 2.24$; $P = .03$) (**Figure 1**). Baseline cognitive scores were similar for those with incident DM compared with participants without DM, although scores tended to be between those with prevalent DM and those without DM. Additional adjustment for time-dependent myocardial infarction and hypertension and baseline body mass index did not significantly alter the relationship between DM and cognitive scores. There was no interaction with race, sex, education, or apolipoprotein E ε4 status and DM on cognitive decline ($P > .05$ for all).

After an average of 9 years, participants with prevalent DM had significantly greater decline on both the 3MS ($t = 2.66$; $P = .008$) and the DSST ($t = 3.69$; $P = .001$) compared with those without DM (Table 2). After adjusting for age, race, sex, and education, these differences remained significant (prevalent DM: mean [SE] 3MS score: –5.6 [0.5]-point decline; $t = 2.37$; $P = .02$; DSST: –7.8 [0.5]-point decline; $t = 2.37$; $P = .001$) compared with participants without DM (3MS: –4.3 [0.3]-point decline; DSST: –5.8 [0.3]-point decline) (Figure 1). Compared with participants without DM, those with incident DM did not have significantly greater decline in scores but demonstrated mean score decline between the other groups.

Among participants with prevalent DM, higher levels of HbA_{1c} were associated with lower 3MS and DSST test scores. Among participants with prevalent DM with an HbA_{1c} value, at a mean follow-up of 3.5 years, those with a mid (7%-8%; n = 219) or high (≥8%; n = 227) HbA_{1c} level had significantly lower mean (SE) scores than those with a low level (≤7%; n = 269) on both the 3MS (3MS: low: 87.1 [0.4]; mid: 86.2 [0.4]; high: 85.7 [0.5]; $F = 8.2$; P for overall = .003) and the DSST (low: 29.5 [0.6]; mid: 29.0 [0.6]; high: 28.0 [0.7]; $F = 3.4$; P for overall = .04) (**Figure 2**). After adjusting for age, race, sex, and education, scores remained significantly lower for the mid and high tertiles on the 3MS but were no longer significant for the DSST ($F = 0.87$; P for overall = .42). Additional adjustment for myocardial infarction, hypertension, and body mass index did not appreciably change results.

COMMENT

In this prospective study of well-functioning older adults, persons with prevalent DM had lower baseline and greater 9-year decline in cognitive scores compared with participants who remained free of DM over the follow-up. Participants who developed DM during follow-up tended to have scores between those without DM and those with prevalent DM but scores were not statistically different from the non-DM group. Decline scores on the 3MS among those with incident DM were also similar to those with prevalent DM. In addition, participants with DM who had a higher HbA_{1c} level performed more poorly on cognitive tests, suggesting that glucose control is related to cognitive function.

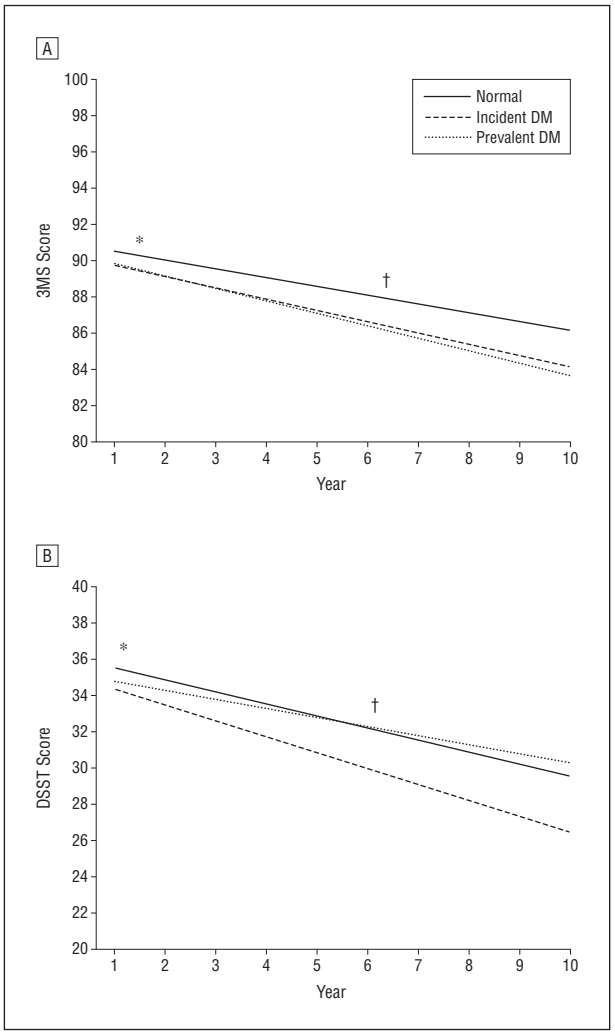

Figure 1. Baseline and 9-year cognitive decline scores by diabetes mellitus (DM) status, adjusting for age, race, sex, and education. A, Modified Mini-Mental State Examination (3MS) scores. *Baseline 3MS score: prevalent DM vs normal, $t = 2.5$; P value = .01; incident DM vs normal, $t = 1.69$; P value = .09. †3MS 9-year decline slope: prevalent DM vs normal, $t = 2.37$; P value = .02. B, Digit Symbol Substitution Test (DSST) scores. *Baseline DSST score: prevalent DM vs normal, $t = 2.24$; P value = .03. †DSST 9-year decline slope: prevalent DM vs normal, $t = 3.25$; P value = .001.

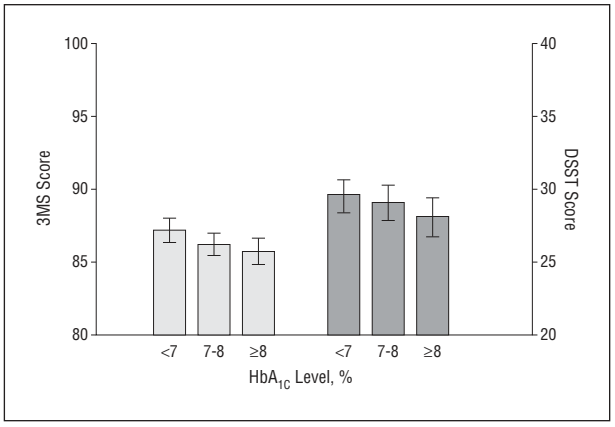

Figure 2. Unadjusted Modified Mini-Mental State Examination (3MS) and Digit Symbol Substitution Test (DSST) scores by glycosylated hemoglobin A_{1c} (HbA_{1c}) level at mean time of follow-up. The error bars indicate standard error.

Our results are consistent with prior studies reporting an association between DM and an increased risk of cognitive impairment.[2,5] A few studies have also investigated cognitive function in the early stages of DM and report a trend toward reduced cognitive function in adults with recently diagnosed DM.[19,20] For example, a prospective study of a group of middle-aged adults (aged 43-70 years) found that, in participants older than 60 years, participants who developed DM during follow-up had greater cognitive decline than those without DM and that those with prevalent DM at the study's baseline had the greatest cognitive decline.[20] Another study in older adults reported small reductions in cognitive function in participants recently diagnosed with DM compared with a non-DM control group.[19] Results from the current study showed a similar trend toward intermediate cognitive decline in older adults with incident DM. This suggests that delaying or preventing the onset of DM may prove beneficial for maintaining cognitive function in older adults, especially considering that a longer duration of DM has been linked to worse cognitive function, including mild cognitive impairment.[21]

Hyperglycemia has been proposed as a mechanism that may contribute to the association between DM and reduced cognitive function.[22] The American Diabetes Association recommends maintaining an HbA_{1c} level of less than 7% to help prevent microvascular complications[23] and our results add to a body of literature that suggests that maintaining an HbA_{1c} value at this level may also help with cognitive health. Higher HbA_{1c} level has been associated with worse cognitive outcomes in both cross-sectional[9,11] and prospective[10,12] studies, but results have been inconsistent.[13,14] For example, in the Rancho Bernardo Study, glycemic control was found to mediate the relationship between DM and cognitive decline[12] but this association was not found in the Atherosclerosis Risk in Communities study.[13] However, participants in the Atherosclerosis Risk in Communities study were younger (mean age, 56 years) and may have been less likely to experience cognitive decline. In our study, participants with higher levels of HbA_{1c} had lower cognitive scores, strengthening support for an increased risk of cognitive impairment with poor glucose control among older adults with DM. Results from the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes trial also found an association between HbA_{1c} levels and reduced cognitive performance; however, an intensive glycemic control intervention was not shown to benefit cognitive function.[24] Hyperglycemia may contribute to cognitive impairment through such mechanisms as the formation of advanced glycation end products,[25] inflammation,[26] and microvascular disease.[27] However, glycemic control needs to be considered in light of other studies suggesting that hypoglycemia episodes may also be linked to dementia.[28] This suggests elderly individuals with DM should be carefully monitored for optimal care.

There are several other mechanisms that may underlie the association of DM and glucose control and reduced cognitive function. Individuals with DM are at an increased risk for renal disease, depression, stroke, hypertension, hyperlipidemia, and cardiovascular disease, each of which may impair cognitive performance.[29-31] In

our study, adjustment for several comorbidities did not significantly alter the associations between DM and glucose control and reduced cognitive function; however, we cannot rule out residual confounding.

Strengths of this study include a prospective design with a long follow-up period and a relatively large and diverse sample. For incident DM, cognitive function was measured at baseline before the onset of disease. For HbA_{1c} level, we used a cutoff of less than 7% for glycemic control, which has been recommended by the American Diabetes Association to reduce microvascular disease.[23] We were also able to adjust for several potential confounders. The study also had several limitations. The Health ABC study enrolled only well-functioning elderly adults at baseline and results may not be generalized to elderly individuals with functional disabilities. The cognitive test battery was limited to general cognitive function and processing domains. In addition, the differences in cognitive scores between the groups were relatively small and the clinical significance is unclear. Analysis of HbA_{1c} changes over time was restricted because of inconsistency in assays used during different years of Health ABC study follow-up. We did not assess insulin resistance or levels, which may also be related to cognitive function.[32] In addition, because of the small sample size of those with incident DM, our power to detect group differences was restricted. We also did not have information on duration or severity of DM for those with prevalent DM at study baseline.

This study supports the hypothesis that older adults with DM have reduced cognitive function and that poor glycemic control may contribute to this association. Future studies should determine if early diagnosis and treatment of DM lessen the risk of developing cognitive impairment and if maintaining optimal glucose control helps mitigate the effect of DM on cognition.

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