CLINICAL RESEARCH STUDY

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Glycemia and Cognitive Function in Metabolic Syndrome and Coronary Heart Disease

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ABSTRACT

OBJECTIVE: Higher hemoglobin A_{1c} (HbA_{1c}) is associated with lower cognitive function in type 2 diabetes. To determine whether associations persist at lower levels of dysglycemia in patients who have established cardiovascular disease, cognitive performance was assessed in the Targeting INflammation Using SALsalate in CardioVascular Disease (TINSAL-CVD) trial.

METHODS: The age-adjusted relationships between HbA_{1c} and cognitive performance measured by the Mini-Mental State Examination, Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, Trail Making Test, and Categorical Verbal Fluency were assessed in 226 men with metabolic syndrome and established stable coronary artery disease.

RESULTS: Of the participants, 61.5% had normoglycemia, 20.8% had impaired fasting glucose, and 17.7% had type 2 diabetes. HbA_{1c} was associated with cognitive function tests of Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, Trail Making Test, and Categorical Verbal Fluency (all $P < .02$), but not the Mini-Mental State Examination. In an age-adjusted model, a 1% (11 mmol/mol) higher HbA_{1c} value was associated with a 5.9 lower Digit Symbol Substitution Test score (95% confidence interval [CI], −9.58 to −2.21; $P < .0001$); a 2.44 lower Rey Auditory Verbal Learning Test score (95% CI, −4.00 to −0.87; $P < .0001$); a 15.6 higher Trail Making Test score (95% CI, 5.73 to 25.6; $P < .0001$); and a 3.71 lower Categorical Verbal Fluency score (95% CI, −6.41 to −1.01; $P < .02$). In a multivariate model adjusting for age, education, and cardiovascular covariates, HbA_{1c} remained associated with cognitive function tests of Rey Auditory Verbal Learning Test ($R^2 = 0.27$, $P < .0001$), Trail Making Test ($R^2 = 0.18$, $P < .0001$), and Categorical Verbal Fluency ($R^2 = 0.20$, $P < .0001$), although association with the Digit Symbol Substitution Test was reduced.

CONCLUSIONS: Higher HbA_{1c} is associated with lower cognitive function performance scores across multiple domain tests in men with metabolic syndrome and coronary artery disease. Future studies may demonstrate whether glucose lowering within the normative range improves cognitive health.

KEYWORDS: Cardiovascular disease; Cognitive function; Glycemia; Hemoglobin A_{1c}

Mild cognitive impairment is common and may precede frank dementia. Approximately 19% of persons aged more than 65 years and 29% aged more than 85 years have mild cognitive impairment,[1] representing a substantial population health issue among older persons. Persons with coronary artery disease and those with type 2 diabetes are both at higher risk of cognitive impairment.[2-4] More patients with cardiovascular disease have dysglycemia, diabetes, or prediabetes than normoglycemia.[5]

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Cognitive function is associated with glycemia in patients with type 1 or 2 diabetes.[6-8] Cognitive function declines with acute hyperglycemia[9] or hypoglycemia.[10,11] Working memory may improve in patients with type 2 diabetes with improving metabolic control.[12] The Memory in Diabetes (MIND) substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial established an association between higher age-adjusted hemoglobin A$_{1c}$ (HbA$_{1c}$) and lower cognitive function in patients with type 2 diabetes[13] at high cardiovascular risk and with HbA$_{1c}$ >7.5% (58.5 mmol/mol) at study entry. Because dysglycemia is highly prevalent in patients with cardiovascular disease, we sought to determine whether the association between glucose and cognitive dysfunction was also present at lower levels of dysglycemia than in the ACCORD study population, because this could have a substantial impact on the general health of patients with coronary heart disease, including medication adherence and quality of life. Thus, we evaluated the relationship between HbA$_{1c}$ and cognition in a complementary cohort to the ACCORD-MIND with stable coronary artery disease and HbA$_{1c}$ <7.5% (58.5 mmol/mol), spanning the range from normal to prediabetes and well-controlled diabetes.

CLINICAL SIGNIFICANCE

- Higher hemoglobin A$_{1c}$, a measure of average glucose concentrations over 2 months, is associated with lower cognitive function in those with type 2 diabetes.
- The association between hemoglobin A$_{1c}$ and cognitive function extends into the glycemic range that would be considered nondiabetic to well-controlled diabetes in men with metabolic syndrome and stable coronary artery disease.
- Demonstrating that this relationship occurs is important to understand the pathophysiology and to develop novel therapeutic approaches.

MATERIALS AND METHODS

The study was approved by the Joslin Diabetes Center Institutional Review Board. Subjects provided informed written consent. This study was conducted as an ancillary investigation in the trial Targeting INflammation Using SALsalate in CardioVascular Disease (ClinicalTrials.gov Identifier: NCT00624923). The aim of the parent study is to determine the efficacy of targeting inflammation using salsalate to reduce the progression of noncalcified coronary artery plaque volume assessed by multidetector computed tomography angiography (MDCTA) over 30 months. A sub-aim of the study is to assess the effects of targeting inflammation on cognitive function. Only baseline data were used in this analysis.

Participants include community-dwelling adult men with metabolic syndrome, who are fluent in the English language, who are aged <75 years, with body mass index between 27 and 40 kg/m^2, and with established coronary artery disease, including previous myocardial infarction or coronary artery bypass, stable angina, abnormal cardiac exercise or pharmacologic stress test, or plaque by prior imaging in at least 1 coronary artery. All participants were using statin class agents and had an estimated Cockcroft–Gault creatinine clearance >60 mL/min.[14] Persons with prior stroke, malignancy, tinnitus, gastric bypass surgery, gastrointestinal bleeding, alcohol use exceeding 14 units/week, and use of chronic thiazolidinediones, insulin, glucagon-like peptide-1 agonists, corticosteroids, nonsteroidal anti-inflammatory drugs, warfarin, or uricosuric agents were excluded from the parent study. Women represent <6% of the parent study population, so they were excluded from substudy analysis. Participants with poor glycemic control (HbA$_{1c}$ >7.5%; 58.5 mmol/mol) were excluded a priori to maintain the focus of investigation on persons with normal to moderate dysglycemia. The mean of 3 blood pressure measurements was used. Blood was collected after overnight fast for HbA$_{1c}$, glucose, lipids, and creatinine (Quest Laboratories, Cambridge, Mass). Table 1 summarizes the cognitive measurement tools performed by a trained study coordinator after participants had a light standardized meal.

Statistical Methods

Linear regression was used to assess the relationship of each measure of cognitive status with HbA$_{1c}$ and to control for potential confounding factors, including age, education, smoking status, body mass index, blood pressure, non–high-density lipoprotein cholesterol, Short Form 36 Mental Score, and history of depression. The age-adjusted relationship between HbA$_{1c}$ and cognitive measure was the primary end point (model 1). The age-adjusted analysis was repeated in a subset excluding those with type 2 diabetes (model 2). Model 3 included age and education adjustment. Model 4 included all the covariates just listed. Beta-coefficient estimates are provided with 95% confidence limits and as standardized estimates. P values < .05 were considered significant. All analyses were performed using SAS 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Demographic and clinical characteristics of study participants are described in Table 2. Of the participants, 61.5% had normoglycemia, 20.8% had impaired fasting glucose, and 17.7% had type 2 diabetes. 97.3% of participants had normal cognition based on Mini-Mental State Examination scores of ≥25, and no participant had scores consistent with moderate or severe dementia. HbA$_{1c}$ was not associated with the Mini-Mental State Examination score in any model. However, in bivariate analysis, HbA$_{1c}$

Table 1 Cognitive Function Tests Administered

Cognitive Function Test	Acronym	Test Assessment	Scoring
Mini-Mental State Examination	MMSE	Brief screen for dementia, orientation to time and place, memory, attention, calculation, language, and visual-spatial skills	No. of correctly completed questions or problems answered correctly of possible total of 30
Digit Symbol Substitution Test	DSST	Psychomotor performance, including sustained attention, response speed, and visuo-motor coordination	No. of symbols correctly matched with their corresponding digit in 1 min
Rey Auditory Verbal Learning Test	RAVLT	Immediate verbal memory and learning	Average no. of words recalled (0-15) over the immediate (reported as sum of 4 trials), short, and delayed recall trials
Trail Making Test	TMT	Complex visual scanning, attention, and ability to shift between tasks	Subject must first connect consecutively numbered circles (Part A) and then connect the same number of consecutively numbered and lettered circles alternating between the 2 sequences (Part B)
Categorical Verbal Fluency	CVF	Language, memory, and fluency of speech	No. of items from each category (animals and supermarket items) named in 60 sec
Short Form 36 Health Survey	SF-36	Patient-reported outcomes of health reflecting aspects of physical function, mental health, and quality of life	Self-administered 36-question survey

A description of the cognitive function tools, functional domains evaluated in the tests, and scoring process is provided.[29]

was associated with scores on Digit Symbol, Rey Auditory Verbal Learning Test Word Learning, Trail Making B and Categorical Verbal Fluency (all $P < .02$) (Figure 1). In models including HbA_{1c} and age (the primary end point) (Table 3, model 1), the variance explained by the models for these 4 cognitive tests improved compared with HbA_{1c} alone, and higher HbA_{1c} remained associated with lower cognitive function. Specifically in the age-adjusted model for the full population, a 1% higher HbA_{1c} value was associated with a 5.9 lower Digit Symbol score (95% confidence interval [CI], −9.58 to −2.21; $P < .0001$); 2.44 lower Rey Auditory Verbal Learning Test Word Learning score (95% CI, −4.00 to −0.87; $P < .0001$); 15.6 higher Trail Making B score (95% CI, 5.73-25.6 $P < .0001$); and 3.71 lower Categorical Verbal Fluency test score (95% CI, −6.41 to −1.01; $P < .02$). When considering only the subcohort without diabetes, in age-adjusted models, higher HbA_{1c} remained associated with lower cognitive function in Digital Symbol, Rey Word Learning, and Trail Making B scores, although significance was not retained for Categorical Verbal Fluency (Table 3, model 2).

Likewise, in models adjusting for age and education (Table 3, model 3), the model predictive values were improved for these 4 cognitive tests compared with HbA_{1c} alone, and HbA_{1c} as a covariate remained associated with cognitive function, with the exception of Categorical Verbal Fluency, for which significance for HbA_{1c} was reduced.

In a model adjusted for age, education, and cardiovascular and depression covariates (Table 4, model 4), HbA_{1c} remained associated with cognitive function tests of Rey Word Learning, Trail Making, and Categorical Verbal Fluency (all $P < .0001$), although association with Digital Symbol score was reduced. Furthermore, in standardized parameter estimates, HbA_{1c} was the top ranking covariate, after age and education, associated with cognitive function for each test.

In contrast, although there was an association in unadjusted analysis between HbA_{1c} and cognitive functions captured by the Rey Auditory Verbal Learning Test immediate recall (sum of 4 trials, Figure 1C), Short Delay for List A ($R^2 = 0.0284$, $P = .011$), and Delay Recall for List A ($R^2 = 0.0216$, $P = .027$), the association between the HbA_{1c} and the delayed components did not remain significant when considering age, education, and cardiovascular and depression covariates.

Fasting glucose on the morning of testing was correlated with the Digit Symbol Substitution Test ($R^2 = 0.032$, $P = .006$) and Trail Making A score ($R^2 = 0.025$, $P = .02$), but not the other test components or the Mini-Mental State Examination. In age-adjusted models, fasting glucose on the morning of testing remained associated with the Digit Symbol Substitution Test score (95% CI, −0.21 to −0.01; $P = .028$), but the association was lost when other covariates were added .

DISCUSSION

We demonstrate an association between cognitive function and glycemia assessed by HbA_{1c} in men with stable coronary artery disease spanning a range from normal to moderately abnormal glucose metabolism. Age and education are important determinants of cognitive function,[15] and the association between cognitive function and glycemia

Table 2 Baseline Characteristics of Targeting INflammation Using SALsalate in CardioVascular Disease Male Participants with Cognitive Function Tests

Variable	Result	Conventional Unit
N	226	
Male Sex (%)	226 (100.0)	
Race/Ethnicity		
- Caucasian	212 (93.8)	
- African American	4 (1.8)	
- Asian	5 (2.2)	
- Multiracial	5 (2.2)	
Age (y)	61 ± 6.9	
Weight (kg)	96.9 ± 12.0	
BMI (kg/m^2)	31.4 ± 3.0	
Waist Circumference (cm)	107.7 ± 8.6	
Blood Pressure		
- Systolic (mm Hg)	128 ± 12.7	
- Diastolic (mm Hg)	75 ± 8.0	
- Mean arterial pressure (mm Hg)*	93 ± 8.5	
- Heart rate (beats/min)	61 ± 9.6	
Glycemia†		
- Normal glucose tolerance	139 (61.5)	
- Impaired fasting glucose	47 (20.8)	
- Type 2 diabetes	40 (17.7)	
Cardiac Risk Factor History		
- Hypertension	153 (67.7)	
- High LDL cholesterol	200 (88.5)	
- Low HDL cholesterol	173 (76.6)	
- High triglycerides	140 (62.0)	
- Smoking Status‡		
o Current smoker	37 (16.4)	
o Former smoker	64 (28.3)	
o Nonsmoker	125 (55.3)	
Medical/Surgical History		
- Coronary Heart Disease		
o Previous myocardial infarction	141 (62.4)	
o Stable angina	89 (39.4)	
o Angioplasty/stent	152 (67.3)	
o Previous coronary artery bypass surgery	54 (23.9)	
o Abnormal exercise tolerance test	88 (38.9)	
o Significant noncalcified plaque	5 (2.21)	
- Vascular Disease		
o Stroke	4 (1.8)	
o Transient ischemic attack	3 (1.3)	
o Carotid vascular disease	6 (2.7)	
o Carotid endartectomy	3 (1.3)	
o Peripheral vascular disease	9 (4.0)	
o Peripheral artery bypass surgery	3 (1.3)	
o Peripheral artery angioplasty	3 (1.3)	
- Psychological§		
o Depression	37 (16.4)	
o Counseling for psychologic problems	25 (11.1)	
o Medicines for psychologic problems	22 (9.8)	
o Anxiety	9 (4.0)	
Years of School Completed		
- 11-14	71 (31.7)	
- 15-18	116 (51.8)	
- 19-22	31 (13.8)	
- 23-26	6 (2.7)	
- Unknown	2 (0.9)	
Laboratory Results		
- Glucose (mmol/L)	5.49	99.0 ± 18.1 (mg/dL)
- HbA_{1c} (mmol/mol)	41.0	5.9 ± 0.49 (%)
- Lipid Profile (mmol/L)		
o Total cholesterol	3.90	150.8 ± 31.1 (mg/dL)
o HDL cholesterol	1.14	44.1 ± 11.3 (mg/dL)
o LDL cholesterol	2.03	78.4 ± 25.7 (mg/dL)
o Triglycerides	1.63	144.1 ± 90.3 (mg/dL)
o Non-HDL cholesterol‖	5.9	106.7 ± 29.7 (mg/dL)
- Serum Creatinine (mg/dL)	84.9	0.96 ± 0.17 (mg/dL)
- Estimated Creatinine Clearance (mL/s)¶	1.90	114.0 ± 27.4 (mL/min)
- Microalbumin Creatinine Ratio		
o Normal (<3.39 mg/mmol creatinine)#	214 (95.5)	
o Microalbuminia (3.39-33.8 mg/mmol creatinine)**	10 (4.5)	
SF-36 Health Survey Score		
- Physical Health (0-100)	81 (73-88)	
- Mental Health (0-100)	86 (78-90)	
- Total SF-36 (0-100)	86 (79-91)	
Cognitive Function		
- Mini-Mental State Examination	29 (28-30)	
- Digit Symbol Substitution Test	61 (53-71)	
- Rey Auditory Verbal Learning Test		
o Sum of the first 4 trials on list A	30 (26-35)	
o Short delay for list A	6 (5-8)	
o Delayed recall of list A	6 (5-8)	
o Delayed recognition of list A	23 (22-24)	

Table 2 Continued

Variable	Result	Conventional Unit
- Trail Making Tests		
o Trail A (in seconds)	29 (24-36)	
o Trail B (in seconds)	72 (57-100)	
- Categorical Verbal Fluency		
o Score 1 — Sum of animals	20 (17-24)	
o Score 2 — Sum of supermarket items	25 (21-29)	
o Score 3 — Sum of score 1 and score 2	45 (39-52)	
o Score 4 — Average of score 1 and score 2	23 (20-26)	

Continuous data are presented as the mean and standard deviation or median (25th-75th percentile) and interquartile range, and categoric data are presented as counts and percentages.

BMI = body mass index; LDL = low-density lipoprotein; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; SF-36 = Short Form 36.

*Mean arterial pressure: [(2*diastolic) + systolic]/3.

†Normal glucose tolerance determined by fasting glucose <5.55 mmol/L (100 mg/dL) and HbA_{1c} <6.5% (47.5 mmol/mol); impaired fasting glucose determined by fasting glucose between 5.55 mmol/L and 6.94 mmol/L (100-126 mg/dL) and HbA_{1c} <6.5% (47.5 mmol/mol); and type 2 diabetes determined by medical history of diagnosis or fasting glucose ≥6.94 mmol/L (126 mg/dL) or HbA_{1c} ≥6.5% (47.5 mmol/mol).

‡Smoking: if stopped ≥15 years, then not a smoker.

§Self-reported: medical history self-report of psychologic conditions.

||Non-HDL cholesterol = total cholesterol − HDL cholesterol.

¶Cockroft—Gault creatinine clearance = ([140-age] × weight [kg])/plasma creatinine × 72 for men (normal 95-145 mL/min).

#Urine albumin to creatinine ratio <30 µg/mg.

**Urine albumin to creatinine ratio 30-299 µg/mg.

remains significant in age-adjusted and age- and education-adjusted models. HbA_{1c} remains associated with cognitive function when cardiovascular risk factors, depression, and Short Form 36 mental status are also included in the model. These findings are important given the increased prevalence of prediabetes and diabetes, cardiovascular disease, and cognitive impairment ranging from mild to frank dementia in the elderly, and the negative role that cognitive impairment in patients with mild dysglycemia could play on individual capacity to adhere to complex cardiovascular treatment recommendations, together providing substantial importance to identify therapeutic targets for the treatment and prevention of cognitive decline.

Vascular dementia may contribute substantially to cognitive decline, both in those with coronary artery disease and type 2 diabetes.[2,3] In addition, approximately 5% of adults aged 65 to 74 years and 50% of adults aged 85 years or more in the United States have Alzheimer's disease.[16] Approximately 22% of the same population (aged 65-74 years) has been diagnosed with diabetes, and the prevalence of abnormal glucose tolerance is substantially higher when including those with undiagnosed diabetes and prediabetes.[17] The 2 disorders frequently co-occur, and type 2 diabetes has been associated with cognitive impairment,[6-8,13] accelerated cognitive decline,[18-20] and higher risk of Alzheimer's disease.[21-23] Furthermore, cognitive impairment less severe than dementia may impair quality of life and independence. Thus, it is of public health importance to better understand the relationship between glycemia and cognitive function, especially in persons with coronary artery disease, in whom multiple mechanisms may contribute to impaired function.

Acute hypoglycemia has been associated with reduced mental function.[10] Likewise, increased glycemia has been associated with poorer cognitive function. In longitudinal analysis, self-reported diabetes was associated with incident all-cause, amnestic, and nonamnestic mild cognitive impairment.[24] Longer duration and severity of diabetes are important determinants of mild cognitive impairment.[8] The ACCORD-MIND demonstrated an age-adjusted association between HbA_{1c} and cognitive function in patients with a mean diabetes duration of 10 years and HbA_{1c} >7.5% (58.5 mmol/mol) at study entry, with a mean of 8.3% (67.2 mmol/mol).[13] Our studies extend the association between HbA_{1c} and cognitive dysfunction into more modest degrees of dysglycemia (<7.5%, 58.5 mmol/mol) in men with metabolic syndrome and stable coronary artery disease to levels that would be considered nondiabetic to medically well controlled diabetes.

We found associations between age and education with cognitive function, consistent with studies in the general population and in those with diabetes.[15,25,26] Our studies are consistent with those showing an association between HbA_{1c} and cognitive function in type 2 diabetes,[8,13,15,27] and in prediabetes and well glycemic-controlled diabetes,[28] but extend these findings into a population with established coronary heart disease. Our study demonstrates the similar strength of association after adjustment for age and education between HbA_{1c} multiple cognitive domains as captured by scores for Digital Symbol, Rey Word Learning Test, and Trail Making B, but less strong association with Categorical Verbal Fluency. Also, 72% to 96% of the strength of association between HbA_{1c} and cognitive function in unadjusted analysis is retained when adding age to the model, and 48% to 64% is retained when both age and education are considered. Moreover, in the subcohort without diabetes, HbA_{1c} remained associated with the Digital Symbol Substitution Test, Rey Auditory Verbal Learning Test, and Trail Making B, although it did not remain associated with Categorical Verbal Fluency. This may be due to reduced power in this smaller group, suggested by the relatively similar beta and standardized estimates compared with the full cohort. It is also possible that cognitive performance in this test of verbal production, semantic memory, and language[29] is not associated with HbA_{1c}, as suggested by reduced association in the model including age, education, and cardiometabolic variables and the analysis limited solely to the nondiabetic HbA_{1c} glycemic range.

Multiple cognitive tests were administered, and higher HbA_{1c} was related to poorer performance across multiple

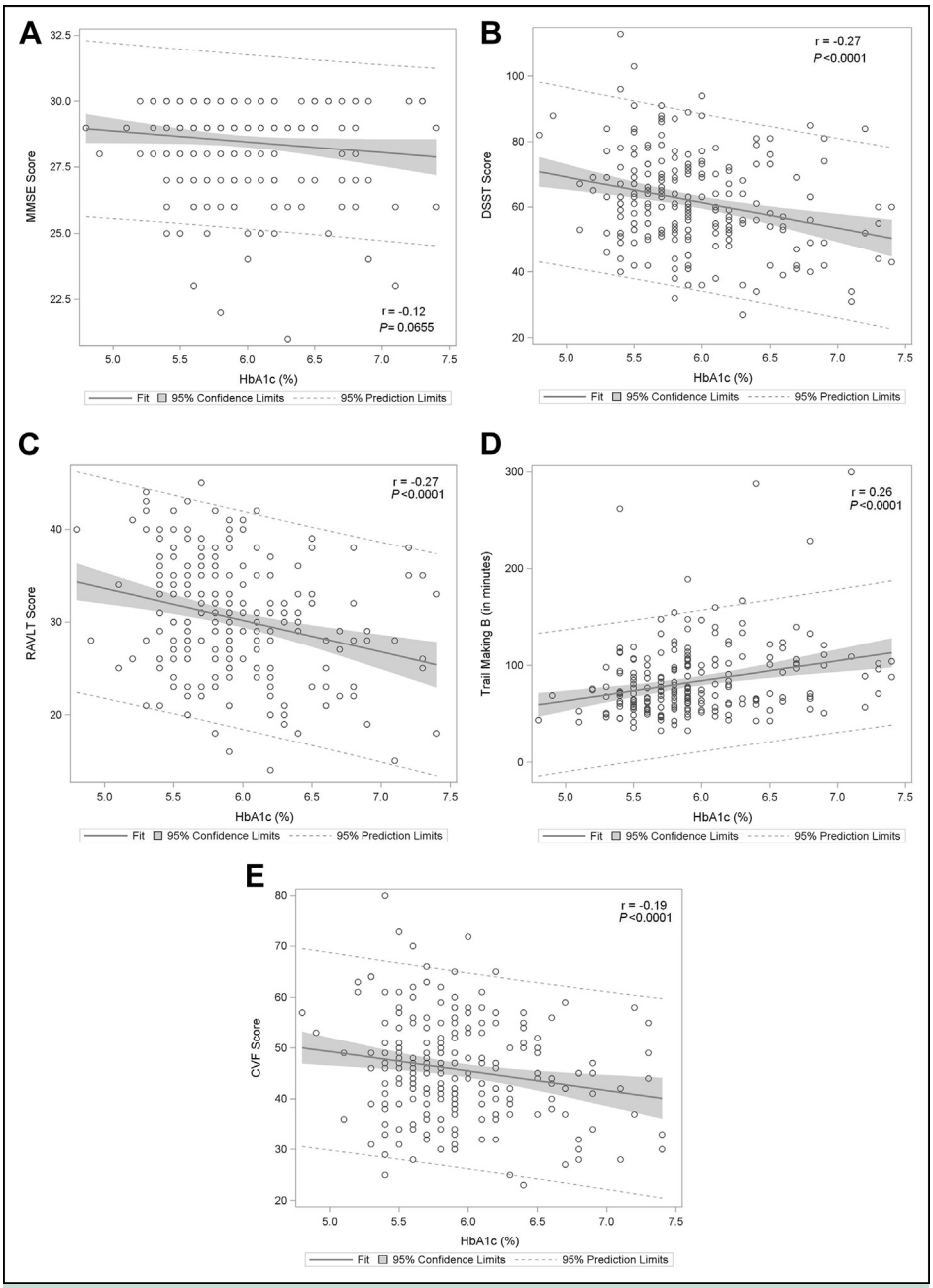

Figure 1 The full study cohort population scatterplots showing correlation, fitted regression, and 95% CIs relating HbA$_{1c}$ and cognitive function tests. (**A**) Displays the fit plot for regression of Mini-Mental State Examination and HbA$_{1c}$. There is no association between HbA$_{1c}$ and Mini-Mental State Examination score ($P = .066$). (**B**) Displays the fit plot regression for Digit Symbol Substitution Test and HbA$_{1c}$. The average Digit Symbol Substitution Test score of a patient changes by $\widehat{\beta} = -7.79$ units for each unit change in HbA$_{1c}$ ($r = -0.27$, $P < .0001$). (**C**) Displays the fit plot for regression of Rey Auditory Verbal Learning Test and HbA$_{1c}$. The average Rey Auditory Verbal Learning Test score of a patient changes by $\widehat{\beta} = -3.44$ units for each unit change in HbA$_{1c}$ ($r = -0.27$, $P < .0001$). (**D**) Displays the fit plot for regression of Trail Making B and HbA$_{1c}$. The average Trail Making B score of a patient changes by $\widehat{\beta} = 20.6$ units for each unit change in HbA$_{1c}$ ($r = 0.27$, $P < .0001$). (**E**) Displays the fit plot for regression of Categorical Verbal Fluency and HbA$_{1c}$. The average Categorical Verbal Fluency score of a patient changes by $\widehat{\beta} = -3.82$ units for each unit change in HbA$_{1c}$ ($r = -0.19$, $P = .0042$). To convert HbA$_{1c}$: HbA$_{1c}$ (%) = [0.09148 * HbA$_{1c}$ (mmol/mol)] + 2.152. CVF = Categorical Verbal Fluency; DSST = Digit Symbol Substitution Test; HbA$_{1c}$ = hemoglobin A$_{1c}$; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test.

Table 3 Relationship Between Cognitive Function Tests and Hemoglobin A_{1c} in Multivariate Analysis Adjusted for Age, and Age and Education

Model 1: Age-Adjusted Model (Full Study Cohort)

Outcome Variable	R^2	Model *P* Value	Covariates	β (95% CI)	Standardized Estimate	Covariate *P* Value
MMSE	0.06	.0013	HbA_{1c}	−0.23 (−0.68 to 0.22)	−0.07	.313
			Age	−0.05 (−0.08 to −0.02)	−0.21	.002
DSST	0.13	<.0001	HbA_{1c}	−5.90 (−9.58 to −2.21)	−0.20	.002
			Age	−0.52 (−0.79 to −0.26)	−0.26	.0001
RAVLT	0.17	<.0001	HbA_{1c}	−2.44 (−4.00 to −0.87)	−0.19	.002
			Age	−0.28 (−0.39 to −0.17)	−0.31	<.0001
Trail Making B	0.13	<.0001	HbA_{1c}	15.6 (5.73-25.6)	0.20	.002
			Age	1.37 (0.67-2.08)	0.25	.0001
CVF	0.04	.0160	HbA_{1c}	−3.71 (−6.41 to −1.01)	−0.18	.007
			Age	−0.03 (−0.22 to 0.16)	−0.02	.750

Model 2: Age-Adjusted Model (Study Population Excluding Type 2 Diabetes)

Outcome Variable	R^2	Model *P* value	Covariates	β (95% CI)	Standardized Estimate	Covariate *P* Value
MMSE	0.04	.036	HbA_{1c}	−0.48 (−1.28 to 0.31)	−0.09	.23
			Age	−0.03 (−0.07 to 0.003)	−0.14	.08
DSST	0.09	.0002	HbA_{1c}	−7.28 (−14.2 to −0.41)	−0.16	.0378
			Age	−0.42 (−0.73 to −0.11)	−0.20	.0075
RAVLT	0.13	<.0001	HbA_{1c}	−3.51 (−6.4 to −0.61)	−0.18	.0179
			Age	−0.23 (−0.36 to −0.10)	−0.26	.0006
Trail Making B	0.10	.0001	HbA_{1c}	17.4 (0.29-34.6)	0.15	.0463
			Age	1.18 (0.41-1.95)	0.23	.0029
CVF	0.02	.22	HbA_{1c}	−4.07 (−9.11 to 0.98)	−0.12	.11
			Age	−0.02 (−0.25 to 0.21)	−0.01	.86

Model 3: Age -and Education-Adjusted Model (Full Study Cohort)

Outcome Variable	R^2	Model *P* Value	Covariates	β (95% CI)	Standardized Estimate	Covariate *P* Value
MMSE	0.09	<.0001	HbA_{1c}	−0.098 (−0.55 to 0.36)	−0.03	.673
			Age	−0.06 (−0.09 to −0.03)	−0.24	.001
			Education	0.11 (0.03-0.19)	0.19	.003
DSST	0.23	<.0001	HbA_{1c}	−3.88 (−7.46 to −0.31)	−0.13	.033
			Age	−0.60 (−0.85 to −0.35)	−0.29	<.0001
			Education	1.63 (1.03-2.23)	0.32	<.0001
RAVLT	0.24	<.0001	HbA_{1c}	−1.65 (−3.18 to −0.13)	−0.13	.033
			Age	−0.31 (−0.42 to −0.22)	−0.35	<.0001
			Education	0.58 (0.33-0.84)	0.27	<.0001
Trail Making B	0.15	<.0001	HbA_{1c}	13.2 (3.17-23.3)	0.17	.010
			Age	1.51 (0.78-2.19)	0.27	<.0001
			Education	−2.08 (−3.96 to −0.56)	−0.15	.016
CVF	0.16	<.0001	HbA_{1c}	−2.34 (−4.93 to 0.25)	−0.11	.079
			Age	−0.10 (−0.28 to 0.08)	−0.07	.284
			Education	1.27 (0.83-1.70)	0.36	<.0001

CI = confidence interval; CVF = Categorical Verbal Fluency; DSST = Digit Symbol Substitution Test; HbA_{1c} = hemoglobin A_{1c}; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test.

functional domains, including aspects of executive function, speed of processing, and language. Although digit substitution and the auditory-verbal learning component Rey Auditory Verbal Learning Test were associated with glycemia, we found only weak association between HbA_{1c} and the memory component in the Rey Auditory Verbal Learning Test (short delay or delay recall), which did not remain significant when adjusted for covariates, and no association was found between HbA_{1c} and the memory component of the Mini-Mental State Examination. These findings are consistent with studies showing the strongest associations between poor glucose tolerance

Table 4 Relationship Between Cognitive Function Tests and Hemoglobin A$_{1c}$ in Multivariate Analysis Adjusted for Age, Education, and Coronary Risk Factors

Model 4: Fully Adjusted Model (Full Study Cohort)

Outcome Variable	R^2	Model *P* Value	Covariates	β (95% CI)	Standardized Estimate	Covariate *P* Value
MMSE	0.11	<.0035	HbA$_{1c}$	−0.15 (−0.63 to 0.33)	−0.04	.539
			Age	−0.06 (−0.09 to −0.03)	−0.24	.001
			Education	0.10 (0.02-0.18)	0.17	.014
			Mean arterial pressure	0.01 (−0.02 to 0.04)	0.06	.408
			Non-HDL cholesterol	−0.00 (−0.01 to −0.01)	−0.00	.991
			Smoking status	0.03 (−0.28 to 0.34)	0.01	.849
			BMI	−0.05 (−0.12 to 0.02)	−0.09	.179
			SF-36 Mental	−0.00 (−0.02 to 0.01)	−0.03	.646
			Depression	−0.06 (−0.66 to 0.55)	−0.01	.851
DSST	0.26	<.0001	HbA$_{1c}$	−3.60 (−7.31 to 0.11)	−0.12	.057
			Age	−0.66 (−0.92 to −0.40)	−0.32	<.0001
			Education	1.57 (0.94-2.20)	0.31	<.0001
			Mean arterial pressure	0.13 (−0.08 to 0.33)	0.07	.23
			Non-HDL cholesterol	−0.05 (−0.11 to 0.01)	−0.11	.08
			Smoking status	0.69 (−1.68 to 3.06)	0.04	.57
			BMI	0.13 (−0.43 to 0.68)	0.03	.66
			SF-36 Mental	0.02 (−0.11 to 0.14)	0.02	.81
			Depression	−2.45 (−7.13 to 2.24)	−0.07	.30
RAVLT	0.27	<.0001	HbA$_{1c}$	−1.58 (−3.16 to 0.01)	−0.12	.049
			Age	−0.32 (−0.43 to −0.21)	−0.36	<.0001
			Education	0.60 (0.33-0.87)	0.28	<.0001
			Mean arterial pressure	0.11 (0.02-0.20)	0.14	.018
			Non-HDL cholesterol	0.00 (−0.02 to 0.03)	0.02	.706
			Smoking status	−0.04 (−1.05 to 0.97)	−0.00	.941
			BMI	−0.13 (−0.37 to 0.11)	−0.06	.283
			SF-36 Mental	0.03 (−0.03 to 0.08)	0.06	.335
			Depression	−0.41 (−2.40 to 1.59)	−0.03	.688
Trail Making B	0.18	<.0001	HbA$_{1c}$	12.0 (1.43-22.5)	0.15	.026
			Age	1.63 (0.90-2.37)	0.29	<.0001
			Education	−1.79 (−3.57 to −0.01)	−0.13	.049
			Mean arterial pressure	0.42 (−0.16 to 1.01)	0.09	.157
			Non-HDL cholesterol	0.13 (−0.03 to 0.29)	0.10	.121
			Smoking status	−1.50 (−8.22 to 5.22)	−0.03	.661
			BMI	−0.26 (−1.85 to 1.32)	−0.02	.743
			SF-36 Mental	−0.06 (−0.43 to 0.30)	−0.02	.730
			Depression	0.36 (−12.9 to 13.6)	0.00	.957
CVF	0.20	<.0001	HbA$_{1c}$	−2.84 (−5.5 to −0.16)	−0.14	.038
			Age	−0.11 (−0.30 to 0.07)	−0.08	.230
			Education	1.44 (0.99-1.89)	0.41	<.0001
			Mean arterial pressure	0.10 (−0.05 to 0.24)	0.08	.211
			Non-HDL cholesterol	0.01 (−0.03 to 0.06)	0.04	.509
			Smoking status	−1.62 (−3.3 to 0.09)	−0.12	.063
			BMI	0.16 (−0.24 to 0.57)	0.05	.428
			SF-36 Mental	−0.02 (−0.11 to 0.08)	−0.02	.735
			Depression	−2.44 (−5.81 to 0.94)	−0.09	.156

BMI = body mass index; CVF = Categorical Verbal Fluency; DSST = Digit Symbol Substitution Test; HbA$_{1c}$ = hemoglobin A$_{1c}$; HDL = high-density lipoprotein; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; SF-36 = Short Form 36.

and lower verbal fluency, although others have not found this relationship in persons with impaired glucose tolerance.[30]

Of note, our study cohort did not have dementia, so associations with mild to moderate dementia would not be detectable. The ranges of cognitive test scores in our cohort are similar to those in a cognitively normal, nondiabetic US sample.[31] The Mini-Mental State Examination was not associated with glycemia in our cohort, similar to studies in persons without dementia.[30] It is possible that associations would be found in cohorts including a greater proportion with compromised cognition.

An association between HbA_{1c} and cognitive function does not establish causality. It is plausible that patients with better cognition also adhere to or make better lifestyle choices and thus have lower HbA_{1c}. It is also possible that HbA_{1c} is a biomarker for severity of vascular disease or other factor(s) influencing cognition. We found a stronger association between HbA_{1c} and fasting glucose on the morning of testing. Our study was limited by the measure of fasting blood glucose and administration of cognitive function testing after a meal, such that immediate measure of immediate glucose concentration during testing is not available. There is no evidence that dietary composition of a preceding meal influences cognitive function.[32] Our findings may not be applicable to women. Statins may be associated with cognitive dysfunction. All participants were using statins, but type and dose varied. Finally, our study was cross-sectional, and we cannot infer on decline.

In our cohort with established coronary heart disease, we found that HbA_{1c} was associated with cognitive function tests of Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, Trail Making, and Categorical Verbal Fluency, but not the Mini-Mental State Examination. Associated tests mainly measure speed of processing, memory, and executive functions.[33] These findings are consistent with reduced neuronal functional connectivity in patients with type 2 diabetes compared with nondiabetic controls in the frontal-parietal and temporal areas of the brain,[34] anatomic areas that mainly relate to cognitive functions of speed of processing, memory, and executive functions,[33] and in white matter and the default-mode network, an area that includes the posterior cingulate cortex and temporoparietal posterior association cortical regions of the brain.[34-36] Higher HbA_{1c} also correlates with reduced hippocampal volume and microstructure.[28] Longer disease duration and elevated fasting blood glucose levels are associated with lower grey matter volume in patients with type 2 diabetes.[20] Our study did not measure brain structure, so whether associations between HbA_{1c} and cognitive function are mediated by structural changes needs further confirmation. However, if hyperglycemia leads to differences in brain structure, it is important to consider that it may not be possible to recover function after chronic exposure that has caused structural change to the adult brain.

Multiple cellular and molecular mechanisms may underlie structural changes in the brain or the relationship between HbA_{1c} and cognitive impairment, including direct or indirect effects of dysglycemia on vascular disease, glycation products that may alter signal transduction pathways or metabolic intermediates,[37,38] neuronal mitochondrial function or oxidative stress, endoplasmic reticulum stress, inflammation, insulin resistance, the effect of insulin degrading enzyme activity on clearance of brain amyloid β,[39-41] or other factors associated with HbA_{1c}.

Accelerated cognitive decline is dependent on both duration of diabetes and glycemic control.[20] The effects of glycemic improvement on cognitive function remain incompletely understood. One study demonstrated improvement over 24 weeks of treatment with sulfonylurea or metformin.[12] In contrast, neither the ACCORD-MIND or the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION) study demonstrated improved cognitive function in the intensive compared with the standard treatment group.[27,42] Hypoglycemia, which was more common in the ACCORD-MIND intensive treatment group compared with standard of care, might have confounded the potential benefits of glucose-lowering. Slower rates of cognitive decline conceivably might occur using antihyperglycemic approaches not associated with hypoglycemia. In the ADDITION trial, both intensive and routine treatment groups had improvement in HbA_{1c}: 7.3% (56.3 mmol/mol) to 6.2% (44.3 mmol/mol) in the intensive treatment group and 7.3% (56.3 mmol/mol) to 6.5% (47.5 mmol/mol) in the control group at baseline and final visit, respectively. The glycemic difference between treatment groups may be insufficient to demonstrate the effects of glycemic lowering on cognitive decline. There were multifactorial metabolic interventions in the ADDITION trial, including antihypertensive and lipid-lowering medications. Statin addition or other factors could confound cognitive improvement. Once cognitive function is lost over extended time, it may not be regained in older adults, so understanding the factors associated with and efforts to prevent early loss remain highly important.

CONCLUSIONS

Higher HbA_{1c} concentrations, even across the range from normal to prediabetes and well-controlled diabetes, are associated with lower cognitive function performance scores across multiple domains in men with metabolic syndrome and cardiovascular disease. Lower cognitive function may affect quality of life and adherence to complex treatment regimens. Future studies may demonstrate whether glucose lowering within the normative range improves cognitive health or prevents progressive decline.

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