CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

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]

Funding: P50HL083813 and P30DK036836.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2014.08.025

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$_{1c}$