

Associations between Markers of Glucose and Insulin Function and Cognitive Function in Healthy African American Elders

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Abstract

Background: Glucose and insulin are important moderators of cognitive function. African Americans have poorer glycemic control across the glycemic spectrum and are at increased risk for type 2 diabetes and poor cognitive health. It is unclear which glucoregulatory markers predict cognitive function in this at-risk population. The purpose of this study was to examine the association between cognitive function and common markers of glucoregulation in non-diabetic African Americans elders.

Methods: Thirty-four, community-dwelling African Americans, aged 50-75 years completed cognitive testing and blood collection as part of a health screening assessment. Cognitive outcomes were composite scores derived from neuropsychological tests of executive function and verbal memory. Linear regression was used to examine relationships between cognitive composite scores and fasting blood levels of glucose, insulin, and hemoglobin A1C, with adjustments for age, education, body mass index, and antihypertensive medication use.

Results: Fasting plasma glucose was negatively associated with executive function ($\beta=-0.41$, $p=0.03$). There was a trend of an association between fasting plasma glucose and verbal memory ($\beta=-0.34$, $p=0.06$). Fasting insulin and hemoglobin A1c were not associated with cognitive function.

Conclusion: High non-diabetic fasting glucose levels were associated with poorer executive function and verbal memory. These results provide preliminary support for proactive glucose control in older African Americans even before glycemic criteria for type 2 diabetes are met. Our findings suggests that high-normal FPG levels may represent an early red-flag to signify increased risk of cognitive impairment or decline.

Keywords: Glucose; Type 2 diabetes; Memory; Executive function; African Americans

Introduction

Type 2 diabetes mellitus (T2DM) is a risk factor for cardiovascular diseases [1], cognitive impairment [2] and dementia [3]. Approximately 30% of adults aged 65 years and older have diabetes; and rates among African Americans are higher than that of many other ethnorracial groups [4]. Similar findings have been reported for rates of dementia among African Americans [5]. Burgeoning evidence shows high-normal glucose levels may be associated with poorer cognitive function [6] and increased risk for cognitive decline [7-8]. Such findings are particularly important for African Americans as this group may experience poorer glycemic control across the glycemic spectrum [9,10].

Executive function and processing speed, cognitive processes mediated by prefrontal brain regions, are particularly vulnerable to glucose and insulin abnormalities [6]. These domains are also among the first to be affected by Alzheimer's disease (AD) [11,12]. Neuroimaging reports show higher fasting glucose is associated with reduced regional cerebral metabolic rate for glucose (rCMRglu) in regions that typically show hypometabolism in AD [13], a finding that replicates some of our earlier work in adults with mild metabolic dysfunction (prediabetes) [14]. Hippocampal and amygdalar atrophy have also been reported in individuals with high-normal FPG levels [15]. Other indices of glucoregulatory function such as fasting insulin and glycosylated hemoglobin A1c (HbA1c) levels, have also been linked to cognitive function. Hyperinsulinemia, a proxy measure of insulin resistance (IR), predicts cognitive decline [16,17]. Elevated insulin levels may also accelerate AD neuropathological processes [18], potentially by disrupting clearance of amyloid- β (A β) [19], the hallmark constituent of

the AD pathology. Glycosylated hemoglobin (HbA1c) is an estimate of long-term glucose control. Studies examining the association between HbA1c and cognitive function have yielded mixed findings [7-8,20]. Disparities in study findings may be influenced by restricted HbA1c variability in non-diabetic populations. Collectively, these findings accentuate the importance of glycemic control, even in the absence of T2DM, to reduce the risk of cognitive impairment and decline.

Given that African Americans are disproportionately affected by T2DM [4] and vulnerable to cognitive decline and dementia [5,21], an investigation that characterizes the relationship between glucose, insulin, and cognitive function, prior to the onset of disease, may help to inform intervention priorities aimed at glycemic control and T2DM prevention rather than T2DM management in this vulnerable population. The current study examined cross-sectional associations between glucoregulatory markers and cognitive function in domains most vulnerable to age-related and disease-related changes in glycemic control (executive function and verbal memory).

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Materials and Methods

Participants

Thirty-four African Americans elders (aged 50-89) who completed health screening for participation in research studies investigating the association between insulin/glucose abnormalities and cognitive aging were included in this study. Recruitment was conducted through advertisements in newspapers, health presentations at local churches and community centers, and blood pressure checks at a predominately African American senior center. Participants were excluded from the study if they had major psychiatric or neurologic disorders, alcoholism, renal or hepatic disease, diabetes mellitus, chronic obstructive pulmonary disease, or unstable cardiac disease. Uses of antihypertensive and cholesterol-lowering medications were permitted while diabetes medications were not. Sample characteristics are provided in Table 1. The institutional review boards of the University of Washington and Veterans Affairs Puget Sound Health Care System approved this study.

Cognitive diagnosis (to rule out dementia) was determined by consensus by an expert panel of physicians and neuropsychologists with experience adjudicating such cases in geriatric populations. All available information from the screening visit was used to make this decision, including cognitive test results, medical and social history, physical examination, and clinical laboratory blood tests. Dementia was an exclusion, and all participants had hemoglobin A1C values <6.5% (threshold for T2DM).

Procedure

Cognitive testing and 12-hr fasting blood collection occurred between 8am and 10am. Measurements in blood included safety labs, glucose and insulin concentration, and HbA1C. Height, weight, and blood pressure measurements were recorded by study personnel.

Cognitive measures

Executive function (EF) was assessed using performance on Trails-B of the Trail-Making Test [22], Digit-Symbol [23], Digit Span Backwards [23], and Verbal Fluency (letter and category) [24]. Verbal

	Females	Males	Total
N	27	7	34
Age, years	60.9 (6.5)	57.5 (7.6)	60.2 (6.7)
Education, years	15.8 (2.3)	14.7 (2.8)	15.2 (2.1)
BMI, m ² /kg	33.8 (6.0)	30.0 (2.5)	33.1 (5.6)
Fasting glucose, mg/dL	94.4 (9.9)	101.4 (4.5)	95.8 (9.4)
Fasting insulin, □U/mL	11.5 (6.3)	12.8 (4.9)	11.7 (6.1)
Hemoglobin A1C, %	5.7 (.29)	5.7 (.19)	5.7 (.27)
3MSE (max=100)	95.8(4.2)	93.2 (3.4)	95.2 (4.1)
Executive Function			
TMT-B, sec	82.6 (30.0)	92.0 (50.0)	84.5 (34.3)
Digit Span Backwards	4.6 (1.4)	4.5 (1.1)	4.6 (1.3)
Digit-Symbol	51.5 (17.3)	46.8 (15.2)	50.4 (16.8)
Word Fluency	34.0 (7.7)	33.1 (3.9)	33.8 (7.0)
Verbal Memory			
CVLT – immediate free recall	9.7 (2.6)	7.8 (4.3)	9.3 (3.1)
CVLT – delayed free recall	10.4 (2.4)	7.2 (4.5)	9.7 (3.1)
Logical Memory – immediate	25.4 (6.6)	21.5 (6.9)	24.6 (6.7)
Logical Memory – delayed	25.8 (7.2)	19.8 (7.4)	24.6 (7.5)

Mean (SD); Abbreviations: BMI: Body Mass Index; 3MSE: Modified Mini-Mental Status Examination; TMT-B: Trail Making Test, part B; Word Fluency: (fluency by letter/3) + (fluency by category); CVLT: California Verbal Learning Test

Table 1: Demographics and cognitive test scores.

memory was assessed using a list-learning task (California Verbal Learning Test, or CVLT), and story recall (Logical Memory of the Wechsler Memory Scale -III) [23]. General cognitive function was assessed using the Modified Mini-Mental State Examination (3MSE) [25]. Raw scores were converted to z-scores using the group mean and standard deviation per test, and z-scores were inverted for Trails-B so that larger scores reflect better performance. The EF composite score was constructed by summing z-scores for Trails-B, Digit-Symbol, Digit Span Backwards, and Fluency, a method used in our previous studies [26]. The verbal memory composite was constructed by summing z-scores for immediate and delayed recall on the CVLT and Logical Memory.

Statistical analysis

Cognitive composite score outcomes were subjected to separate linear regression models by gluco-regulatory marker. Linear regression diagnostics were conducted to test assumptions of linearity, normality, homoscedasticity, and independence of errors, with no violations indicated. Covariates for the regression models included age, education, BMI, and use of antihypertensive medications. Pearson correlations were performed to examine relationships between gluco-regulatory markers and performance on individual cognitive tests. We also explored relationships between cognitive and gluco-regulatory outcomes and the covariates. Although men were underrepresented in this sample (n=7), the results of t-tests failed to indicate any sex-related differences in outcomes. As a consequence, sex was not included as a covariate in the analyses. Statistical significance was set at P<0.05. Statistical analysis was performed using STATA v11.

Results

High-normal FPG levels predicted EF ($\beta=-0.41$, $p=0.03$), such that higher FPG concentrations were associated with lower EF composite scores (Figure 1). Similarly, higher FPG levels tended to be associated with poorer verbal memory, although this relationship failed to reach statistical significance ($\beta=-0.34$, $p=0.06$) (Figure 2). Neither fasting insulin concentrations nor HbA1c predicted executive function or verbal memory performance (all p-values >0.05), (data not shown).

Correlational analyses examining relationships between gluco-regulatory markers and performance on individual cognitive tests indicated that for the CVLT, higher FPG was associated with poorer immediate ($r=-0.39$, $p=0.02$) and delayed recall ($r=-0.38$, $p=0.02$). Similarly, higher FPG predicted worse performance on Digit-Symbol, although this association failed to reach statistical significance ($r=-0.30$, $p=0.06$).

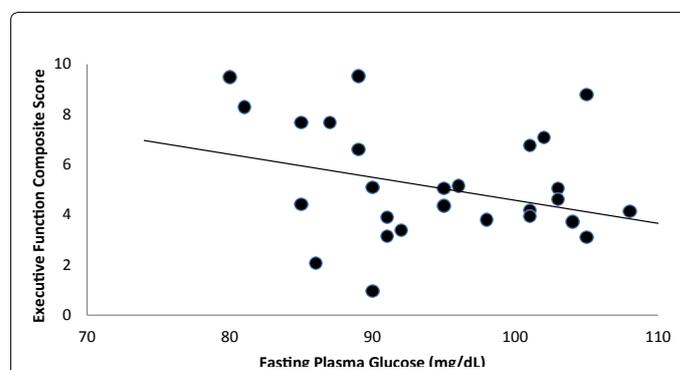
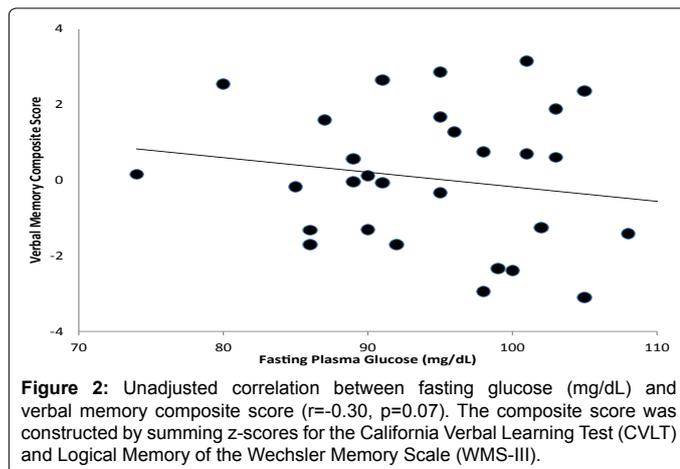


Figure 1: Unadjusted correlation between fasting glucose (mg/dL) and executive function composite score ($r=-0.35$, $p=0.05$). The composite score was constructed by summing z-scores for Trails B of the Trail Making Test, number correct on Digit-Symbol, Digit Span Backwards, and Word Fluency.



Given that nearly 50% of the sample was using antihypertensive medications, we explored whether this exposure differentially impacted the primary finding. The results of an ANOVA on EF composite scores compared across groups defined by antihypertensive use (yes vs. no) and FPG classification (normal vs. impaired: >100 mg/dL) indicated a 2-way interaction ($F(1, 27) = 4.91$, $p=.03$). Executive function composite scores were lower for adults with impaired FPG, but only among non-users of antihypertensives; among users, executive function was comparable for adults with and without impaired FPG. Although antihypertensive users had higher diastolic ($F(1, 32) = 4.81$, $p=.03$) and systolic ($F(1, 32) = 4.91$, $p=.03$) blood pressures, when these measurements were included as covariates in the model, the significant 2-way interaction persisted ($F(1, 25) = 6.04$, $p=.02$). That is, the different impact of FPG on executive function across users and non-users of antihypertensives is not likely attributable to group differences in diastolic or systolic blood pressure.

Discussion

The current study examined the relationship between markers of glucose/insulin function, as measured by FPG, insulin, and HbA1c, and executive function and verbal memory in African American elders, free of T2DM. Our results extend prior empirical findings from predominately White samples by demonstrating that cognitive abilities most vulnerable to T2DM and AD may also be sensitive to variations in FPG even before the threshold of T2DM is crossed [6,27]. This relationship was independent of age, education, BMI, and antihypertensive medication use. In the absence of relationships between fasting insulin, HbA1c, and cognition, our preliminary findings suggest that in African Americans without T2DM, FPG may provide unique and important information about cognitive health.

One biological pathway linking peripheral glucose levels to neurocognitive function is neuroendocrine systems. Brain glucose utilization is regionally heterogeneous and prefrontal brain regions are particularly vulnerable to glucose and insulin related metabolic changes [14,28,29]. Studies of vascular and structural brain-related changes also link peripheral glucose levels to neurocognitive function [30]. Poor glucose regulation is also associated with increased AD neuropathology [31]. Unlike FPG, fasting insulin levels and HbA1c were restricted in range, as might be expected in adults without T2DM, which likely accounted for the absence of associations involving these markers in our study. Other studies documenting a relationship between either HbA1c or fasting insulin and cognition included larger sample sizes and greater variability in insulin and HbA1c ranges [32,33].

We also report antihypertensive medication use may be protective of EF in older African Americans at increased risk for T2DM. To date, only a few studies have examined associations between antihypertensive use, cognitive function, and glycemic control in older adults [34], therefore it remains unclear as to what effect these medications might have on cognition in adults with prodromal T2DM. Hypertension and T2DM commonly co-occur and both conditions are associated with microvascular and macrovascular disease [35]. Moreover, hypertension is independently associated with executive dysfunction [36]. Additional studies are needed to confirm and further explore this finding, such as an interaction involving antihypertensive medication use and executive function in African Americans could have clinically significant implications for clinical care in this cohort.

Limitations of the study include our small sample size, unbalanced gender representation, and cross-sectional design. Also, our estimate of glycemic control was based on a single FPG measurement and therefore may only reflect acute glucose regulatory status. However, our results remain important as FPG is a standard clinical index for screening and management of T2DM, and thus can be a readily accessible tool to identify change in cognitive risk, even before T2DM is diagnosed. Despite these limitations, this study adds to the existing literature. This study examined predictors of cognitive health in a severely understudied cohort of older adults who are at high-risk for T2DM and associated comorbidities, including cognitive impairment. We also utilized robust measures of cognitive function by relying on composite scores that are typically more stable than individual test scores.

In a sample of older African Americans without T2DM, high-normal FPG predicted poorer EF and tended to predict poorer verbal memory, while lower glucose levels were associated with better cognitive performance. Although these findings need to be replicated in larger trials, a critical extension of this work will be to investigate neuropathological correlates of FPG and cognitive function in African Americans without T2DM. These preliminary findings may help inform future trials aimed at prevention strategies to support cognition in prodromal stages of T2DM in minority elders.

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