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Blood glucose levels and cortical thinning in cognitively normal, middle-aged adults

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ABSTRACT

Type II diabetes mellitus (DM) increases risk for cognitive decline and is associated with brain atrophy in older demented and non-demented individuals. We investigated (1) the cross-sectional association between fasting blood glucose level and cortical thickness in a sample of largely middle-aged, cognitively normal adults, and (2) whether these associations were modified by genes associated with both lipid processing and dementia. To explore possible modifications by genetic status, we investigated the interaction between blood glucose levels and the apolipoprotein E (APOE) ε4 allele and the translocase of the outer mitochondrial membrane (TOMM) 40 '523 genotype on cortical thickness. Cortical thickness measures were based on mean thickness in a subset of a priori-selected brain regions hypothesized to be vulnerable to atrophy in Alzheimer's disease (AD) (i.e., 'AD vulnerable regions'). Participants included 233 cognitively normal subjects in the BIOCARD study who had a measure of fasting blood glucose and cortical thickness measures, quantified by magnetic resonance imaging (MRI) scans. After adjustment for age, sex, race, education, depression, and medical conditions, higher blood glucose was associated with thinner parahippocampal gyri ($B = -0.002$; 95% CI -0.004, -0.0004) and temporal pole ($B = -0.002$; 95% CI -0.004, -0.0001), as well as reduced average thickness over AD vulnerable regions ($B = -0.001$; 95% CI -0.002, -0.0001). There was no evidence for greater cortical thinning in ε4 carriers of the APOE gene or in APOE ε3/3 individuals carrying the TOMM40 VL/VL genotypes. When individuals with glucose levels in the diabetic range (≥126 mg/dL), were excluded from the analysis, the associations between glucose levels and cortical thickness were no longer significant. These findings suggest that glucose levels in the diabetic range are associated with reduced cortical thickness in AD vulnerable regions as early as middle age.

1. Introduction

Approximately 28.9 million people in the United States have type II diabetes mellitus (DM), a metabolic disorder characterized by high blood sugar levels (hyperglycemia) in the context of insulin resistance. Older adults are disproportionately affected; it is estimated that nearly 30% of people over the age of 65 have DM and approximately one-quarter of DM cases are undiagnosed [2]. Past research has established that DM is a risk factor for dementia [30], with one study estimating that 6–10% of dementia cases are directly attributable to DM [37]. Further, studies have shown that diabetics have reduced mean cortical thickness and reduced thickness in AD-vulnerable brain regions, measured on magnetic resonance imaging (MRI) scans, compared to non-diabetics with a range of clinical diagnoses from normal to dementia [5,8,45,56]. However, past studies have not examined the relationship of glucose levels and cortical thickness in a cognitively normal, primarily

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middle-aged cohort that is not exclusively a diabetic sample, nor have they examined how genetic factors may impact these associations. To our knowledge, only one study has shown that higher glucose and glycated hemoglobin (HbA1c) levels among middle-aged and older non-demented adults are associated with grey matter atrophy in multiple regions [39]. This study, however, included a small number of patients with a diagnosis of DM, as well as individuals with glucose values in the diabetic range, who may have had undiagnosed diabetes. It therefore remains unclear if associations between glucose levels and cortical thickness only exist for individuals with glucose levels in the diabetic range, or also for individuals with glucose levels in the pre-diabetic and normal range.

Two genes associated with risk for Alzheimer's disease (AD) are of particular relevance to the potential impact of blood glucose on cortical thinning, as they alter lipid and other metabolic pathways [3,33,41]. The apolipoprotein E (APOE) gene is critical for lipid processing and clearance of beta-amyloid (Aβ) from the brain [41]. Compared to the ε2 or ε3 alleles, the ε4 allele is associated with an increased risk of Alzheimer's dementia [19], cognitive decline [6,7], and smaller brain volumes and cortical thinning [18,20]. Further, evidence suggests an interaction between both DM and APOE, such that individuals who have both risk factors have compounded risk for poor cognitive outcomes compared to individuals who have just one of these risk factors [55]. More recently, a poly-T variant rs10524523 or '523 in intron 6 of the translocase of the outer mitochondrial membrane gene (TOMM) 40 '523, which has three allelic length variations – short (S), long (L), and very long (VL) – has also been linked with risk of AD dementia. TOMM40 is hypothesized to impact dementia risk through mitochondrial functioning [3,33]. Research has shown that impaired mitochondrial function leads to reduced glucose uptake in older individuals, and can lead to insulin resistance [36,47]), thus perpetuating the cycle linking TOMM40, DM, and dementia. Compared to the TOMM40 short (S) allele, the very long (VL) allele is associated with earlier onset of Alzheimer's dementia [50], smaller brain volumes, and poorer cognitive performance [21].

Despite evidence linking AD-dementia to both TOMM40 and APOE, as well as to DM, prior studies have not directly examined whether these genotypes alter the association between blood glucose levels and structural brain measures. The goals of the current study, therefore, were two-fold. First, extending findings from previous work [9,10], which focused on volumetric measures of medial temporal regions (e.g., hippocampus, amygdala), the present study examined associations between glucose and cortical thickness in AD-vulnerable regions in a sample that was cognitively normal and largely middle aged. Importantly, our analyses took into account cases of possibly undiagnosed DM. Second, this is the first study, to our knowledge, to examine if the relationship between blood glucose levels and cortical thickness is modified by genetic risk factors for AD. We hypothesized that higher baseline blood glucose would be associated with reduced cortical thickness, particularly in brain regions associated with AD-related atrophy, and that this relationship would be stronger among those with an APOE ε4 allele or the TOMM40 '523 VL/VL genotype.

2. Methods

2.1. BIOCARD study

The data for these analyses come from the BIOCARD Study, which was initiated at the National Institutes of Health (NIH) in 1995 by the Geriatric Psychiatry Branch of the National Institute of Mental Health (PI: Trey Sunderland). It was designed to investigate risk factors for cognitive decline and dementia in a healthy, mainly middle-aged cohort, enriched with those positive for a family history of dementia. The study was discontinued in 2005 for administrative reasons; it was then re-initiated in 2009 at the Johns Hopkins University School of Medicine (PI: Marilyn Albert). To date, approximately 90% of the original participants have been reenrolled [1].

At baseline, participants completed a multi-day evaluation at the Clinical Center of the NIH, which included a clinical and neurological exam, cognitive testing, standard biochemical assays (e.g., potassium, albumin, glucose), and history of current or past medical conditions (e.g., cardiovascular disease, metabolic conditions) and smoking and substance abuse. At enrollment, the majority of participants also underwent an MRI scan of the brain and a lumbar puncture to obtain samples of cerebrospinal fluid (CSF). Annual follow-up exams included a physical and neurological exam and cognitive testing. Details regarding the neuropsychological assessment have been published elsewhere [1]; briefly, the battery includes tests that measure a range of cognitive domains (i.e., memory executive function, language, visuospatial ability, attention, speed of processing, and psychomotor speed). While the study was being conducted at the NIH, participants completed MRI scans and CSF collection every two years.

2.2. Participants

At baseline, participants (n = 349) were primarily middle-aged (mean age = 57.2 years, standard deviation (SD) = 10.3 years). By design, approximately three-quarters of participants had a first-degree relative with dementia. Exclusion criteria included cognitive impairment, and significant medical, psychiatric, or neurological disorders (e.g., severe cardiovascular disease, bipolar disorder, Parkinson's disease, epilepsy, etc.). Informed consent was obtained from all participants.

2.3. Glucose and diabetes measures

Fasting blood glucose was obtained from blood drawn at baseline and at follow-up visits at the NIH Clinical Center. The fasting blood draw and MRI scan (described below) used in the present analyses were performed within a three month period. DM status was ascertained during the clinical exam, during which participants were also asked to report medication use, including DM medication (e.g., Metformin, injectable insulin, etc.). Four participants had a recorded DM diagnosis. An additional 14 participants had blood glucose measures at one or more study visits that were in the diabetic range (≥126 mg/dL) established by the American Diabetes Association [2]). There were 54 individuals with glucose values in the pre-diabetic range (101 to 125 mg/dL).

2.4. Genotyping

APOE genotyping was completed by Athena Diagnostics (Worcester, MA), using restriction endonuclease digestion of polymerase chain reaction (PCR) amplified genomic DNA. For the analyses described below, genotypes were coded dichotomously by APOE ε4 status – those with one or more ε4 alleles (1) and those without an ε4 allele (0).

For TOMM40 genotyping, DNA samples were plated on 96-well plates for long-range PCR and genotyping of the TOMM40-523 poly-T variant, which was performed at Polymorphic DNA Technologies (Alameda, CA, USA); see Roses et al. [50] and Linnertz et al. [40] for further details. Alleles of the TOMM40-523 poly-T variant were classified using the convention established by Roses and colleagues for naming allele lengths: short (S), ≤18 poly-T repeats; long (L) 19–30 repeats; and very long (VL) ≥31 repeats [40,50]. The TOMM40 '523 analyses were also coded dichotomously – those with the VL/VL genotype (1) and those with the S/S genotype (0) (described in more detail under Statistical Analyses, below).

2.5. MRI parameters and cortical thickness measures

MRI scans were completed on a 1.5 Tesla General Electric scanner using a standard multimodal protocol. The scanning protocol included localizer scans, axial Fast Spin Echo sequence (repetition time (TR) = 4250, echo time (TE) = 108, field of view (FOV) = 512 × 512, thickness/gap = 5.0/0.0 mm, flip angle = 90, 28 slices), axial Flair sequence