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Brief communication

Impaired glycemia increases disease progression in mild cognitive impairment

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ABSTRACT

Insulin resistance and type 2 diabetes are associated with cognitive decline and increased risk for Alzheimer's disease (AD). Relatively few studies have assessed the impact of metabolic dysfunction on conversion to AD in mild cognitive impairment (MCI), and it is unclear whether glycemic status is associated with clinically relevant measures of cognitive decline and brain structure in MCI. This study used the Alzheimer's Disease Neuroimaging Initiative database to examine the relationship of baseline glycemia with conversion to AD and longitudinal clinical, cognitive, and imaging measures of decline. Subjects with MCI (n = 264) with baseline and 2-year Clinical Dementia Rating data available were classified according to American Diabetes Association criteria for fasting glucose at baseline. The groups were normoglycemic (fasting glucose, <100 mg/dL; n = 167) or impaired glycemia (fasting glucose, ≥100 mg/dL, n = 97). The impaired glycemia group included individuals with fasting glucose that either reached the American Diabetes Association cut point for impaired fasting glucose or individuals with diagnosed diabetes. Two-year change in Clinical Dementia Rating-Sum of Boxes, cognitive performance testing (global cognition), brain volume (whole-brain and hippocampal volume), fluorodeoxyglucose-positron emission tomography, and conversion to AD were assessed. Subjects with normoglycemia at baseline had less functional (Clinical Dementia Rating-Sum of Boxes) and global cognitive decline over 2 years than subjects with impaired glycemia. Subjects with normoglycemia also lost less whole-brain volume and exhibited lower conversion from MCI to AD. There was no difference in hippocampal volume change or fluorodeoxyglucose-positron emission tomography between groups. These results suggest that baseline glycemia is related to cognitive decline and progression to AD.

1. Introduction

The etiology of sporadic Alzheimer's Disease (AD), the most common type of dementia, remains unknown. However, risk factors for sporadic AD include insulin resistance and type 2 diabetes (De Felice, 2013). The prevalence of both insulin resistance and AD increase with age, and more than half of individuals older than 65 years have either diabetes or prediabetes (Cowie et al., 2006). Thus, an increasing number of individuals will suffer from comorbid AD and type 2 diabetes. It is important to understand not only the effect of impaired glycemia on AD risk, but also on AD progression, beginning in mild cognitive impairment (MCI).

Studies suggest that diabetes may accelerate conversion from MCI to dementia, (Velayudhan et al., 2010; Xu et al., 2010), warranting further study of metabolic dysfunction on cognitive decline in MCI. This report supports and extends prior work using stringent definitions of MCI (amnestic MCI) and impaired glycemia (American Diabetes Association guidelines). Analysis of subjects with MCI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) allowed analysis of clinically relevant outcomes that may contribute to increased conversion, the latest methods for indexing decline, and biomarkers. This study is the largest to examine the relationship between glycemia and disease progression in amnestic MCI. We hypothesized that impaired glycemia would be associated with longitudinal functional, cognitive, and structural changes, and may represent a modifiable risk factor for MCI-to-AD progression.

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2. Methods

2.1. Sample and recruitment

Data were obtained from ADNI (http://adni.loni.usc.edu/) on 5 January 2012. The ADNI is conducted by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, pharmaceutical companies, and nonprofits with the goal of testing whether biologic, neuroimaging, clinical, and neuropsychological assessments can be combined to measure progression to AD. A total of 264 subjects with amnestic MCI and baseline and 24-month Clinical Dementia Rating (CDR) assessments were included. One subject that qualified was excluded because of a very high fasting glucose level (>400 mg/dL). Imaging data (magnetic resonance imaging and fluorodeoxyglucose-positron emission tomography [FDG-PET]) were available for a subset of individuals and were also analyzed.

2.2. Classification of groups

We classified subjects as either having normoglycemia (NG; fasting glucose, ≤99 mg/dL; n = 167) or as having impaired glycemia (IG; fasting glucose, ≥100 mg/dL; n = 97) using American Diabetes Association criteria. Subjects with diagnosed diabetes (n = 4) were classified as IG. For ADNI, subjects with MCI scored 24–30 points (inclusive) on the Mini-Mental State Examination, and had a memory complaint, abnormal memory function (Wechsler Memory Scale-Revised, Logical Memory II score ≤8 points for more than 16 year of education, ≤4 points for 8–15 years of education, ≤2 points for less than 7 years of education), and a CDR of 0.5, and did not meet criteria for dementia.

2.3. Clinical and cognitive assessment

Clinical and neuropsychometric assessment included the CDR and cognitive tests used in the Uniform Data Set. The CDR assessment considered 6 independent domains, (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care), the sum of which is referred to as CDR-Sum of Boxes (Burke et al., 1988). The Uniform Data Set neuropsychological test battery consists of the Mini-Mental State Examination, Logical Memory (I and II), Digit Span Forward and Backward, Category Fluency (animals and vegetables), Trail Making Tests A and B, the Wechsler Adult Intelligence Scale Digit Symbol, and the Boston Naming Test. A Web-based normative calculator (Shirk et al., 2011) was used to compute sex, age, and education-adjusted scores for each test. A global cognition score was generated from the average of all normed scores.

2.4. Laboratory measures and genotyping

Plasma was collected and analyzed for insulin on a 190-analyte multiplex immunoassay panel (Human Discovery Map; Rules-Based Medicine, TX) per ADNI protocol. For this study, only plasma insulin values greater than the assay's least detectable dose for insulin (n = 257) were used; readings less than the least detectable dose (0.66 μU/mL) were excluded. Further information is available from the Biomarkers Consortium Data Primer (http://adni.loni.usc.edu/). Insulin sensitivity (quantitative insulin sensitivity check index) was calculated as described (Katz et al., 2000), with greater values indicative of greater insulin sensitivity. Apolipoprotein ε4 (*APOE* ε4) genotyping was performed at the University of Pennsylvania (ADNI Biomarker Core Laboratory). Subjects were *APOE* ε4 positive if they carried at least 1 allele. Cerebrospinal fluid was analyzed by ADNI for amyloid-β (Aβ) and phosphorylated-tau (p-tau) using the multiplex xMAP Luminex platform (Luminex Corporation, Austin, TX) as described (Shaw et al., 2009).

2.5. Magnetic resonance imaging and FDG-PET scanning

All magnetic resonance imaging and PET analyses were of previously processed secondary data obtained from ADNI. Hippocampal and whole brain volume data from the Anders Dale Lab (University of California, San Diego, CA) were used, and details on their processing methods are published elsewhere (Holland et al., 2009). For normalization, we used total intracranial volumes calculated automatically from FreeSurfer (Fischl et al., 1999). A subgroup of subjects also presented for an FDG-PET scan after a 4-hour fast. A 5.0 ± 0.5 mCi dose of [^{18}F]FDG was injected intravenously, and quantitative imaging was performed over 60 minutes. Mean FDG values were calculated as described (Landau et al., 2011) from the average of 5 regions of interest (bilateral posterior cingulate cortex, right and left inferior temporal region, and right and left lateral parietal region) chosen based on previous studies using FDG-PET in subjects with MCI and AD.

2.6. Statistical analyses

Categorical variables (sex, 2-year conversion, and *APOE* ε4 genotype) were analyzed using the χ^2 test. All other data were analyzed using analysis of variance. Change scores were computed by subtracting the 24-month value from baseline. Age, sex, education, and genotype were included as covariates for all variables except global cognition. Age, sex, and education were included in the calculation of the global cognition z-score, and thus only genotype was included as a covariate. Fasting glucose and fasting insulin values were not distributed normally and were log transformed before analysis.

3. Results

The glycemia groups did not differ in years of education ($F = 0.472$, $p = 0.493$), sex ($\chi^2 = 2.8$, $p = 0.093$), proportion of *APOE* carriers ($\chi^2 = 1.47$, $p = 0.226$), age ($F = 3.5$, $p = 0.061$), body mass index ($F = 1.48$, $p = 0.309$), or body weight ($F = 0.196$, $p = 0.769$). Although there was a trend for a difference in age, it did not reach significance and analyses were corrected for age. Subjects with NG had lower fasting glucose levels and were more insulin sensitive (quantitative insulin sensitivity check index) than subjects with IG ($F = 6.3$, $p < 0.001$). Triglyceride levels were lower in subjects with NG ($F = 3.59$, $p < 0.001$). Fasting insulin ($F = 1.43$, $p = 0.076$) and cholesterol ($F = 7.5$, $p = 0.95$) were not different based on glycemic status. Cerebrospinal fluid Aβ1–42 and p-tau were also not different between groups ($F = 7.0$, $p = 0.298$ and $F = 3.9$, $p = 0.860$, respectively; Table 1). Subjects with IG exhibited a greater increase in CDR-Sum of Boxes scores over 2 years compared with individuals with NG ($F = 3.1$, $p = 0.028$). In addition, decline in global cognition over 2-years was also significantly greater for subjects with IG than subjects with NG; individuals with IG performed more poorly compared with individuals with NG ($F = 3.8$, $p = 0.023$). In line with greater clinical and cognitive decline, subjects with IG exhibited greater conversion from MCI to AD over 2 years (48.5%, 24.3%/y) than subjects with NG (32.3%, 16.2%/y; $\chi^2 = 6.749$, $p = 0.009$; Table 2). Subjects with IG exhibited greater loss of whole-brain volume over 2 years compared with individuals with NG ($F = 4.3$, $p = 0.046$). This was significant only for the whole brain and not the hippocampus ($p = 0.350$). Furthermore, a 2-year change in brain glucose metabolism (global FDG-PET) was not different between groups ($p = 0.695$).