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Featured Article

Glucose level decline precedes dementia in elderly African Americans with diabetes

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Abstract

Introduction: High blood glucose levels may be responsible for the increased risk for dementia in diabetic patients.

Methods: A secondary data analysis merging electronic medical records (EMRs) with data collected from the Indianapolis–Ibadan Dementia project (IIDP). Of the enrolled 4105 African Americans, 3778 were identified in the EMR. Study endpoints were dementia, mild cognitive impairment (MCI), or normal cognition. Repeated serum glucose measurements were used as the outcome variables.

Results: Diabetic participants who developed incident dementia had a significant decrease in serum glucose levels in the years preceding the diagnosis compared to the participants with normal cognition ($P = .0002$). They also had significantly higher glucose levels up to 9 years before the dementia diagnosis ($P = .0367$).

Discussion: High glucose levels followed by a decline occurring years before diagnosis in African American participants with diabetes may represent a powerful presymptomatic metabolic indicator of dementia.

Keywords: Dementia; Alzheimer disease; Longitudinal risk factors; Diabetes; Glucose levels; African Americans; Electronic medical records; Early detection

1. Introduction

With the aging of the United States and world populations, the dementing disorders including Alzheimer disease (AD) are emerging as a major public health challenge. The identification of potentially modifiable risk factors for these disorders is critically important. Vascular risk factors such as diabetes, hypertension, hyperlipidemia, and obesity have been implicated as risk factors for dementia, but the results have not been consistent [1–4].

Rates of diabetes have been increasing worldwide [5] thus the relationship between diabetes and dementia has received particular scrutiny [6–10]. A recent longitudinal study demonstrated that higher glucose levels in elderly participants with or without diabetes were associated with an increased risk of dementia occurring years before the dementia diagnosis [11].

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Most predictive studies of the association of vascular risk factors with dementia have typically used measurements at a single point of time or relied on a mean value of multiple measurements over time. These analytic approaches may fail to capture change or variability in these markers over the lengthy presymptomatic period that precedes a clinical diagnosis of dementia/AD [12].

The Indianapolis Ibadan dementia project (IIDP) is a 20-year National Institute on Aging–funded longitudinal study of dementia and its risk factors in elderly community-dwelling African Americans living in Indianapolis, Indiana and elderly community-dwelling Yoruba living in Ibadan, Nigeria. Recently, data from the African American participants in the study were merged with data from the Indiana Network for Patient Care, a regional health information exchange, allowing us to examine longitudinal vascular risk factor profiles based on diagnostic testing obtained in the routine care of these older adults. This article reports on an analysis of repeated serum glucose measurements and cognitive outcomes for the African American participants.

2. Methods

2.1. Study population

The study population consisted of the African American participants of the IIDP. All were age 65 or older residing in Indianapolis, Indiana. Recruitment was conducted at two time points. During the first recruitment in 1992, 2212 African Americans aged 65 years or older living in Indianapolis were enrolled. In 2001, the project enrolled 1893 additional African American community-dwelling participants 70 years and older. All participants agreed to undergo regular follow-up cognitive assessment and clinical evaluations. Details on the assembling of the original cohort and the enrichment cohort are described elsewhere [13,14].

The study followed a two-stage design with a screening evaluation every 2 to 3 years followed by a more comprehensive home-based clinical evaluation. Diagnoses of dementia, mild cognitive impairment, and Alzheimer disease were made by consensus [15–17]. For more details of the diagnostic process and criteria, see Supplementary Methods 1.

2.2. Electronic medical records

Electronic medical records were obtained from the Indiana Network for Patient Care (INPC). The INPC is a regional health information exchange that integrates clinical information from the five major health care systems in Indianapolis in support of medical care (see Supplementary Methods 2) [18].

EMR data were made available after appropriate approvals from the INPC privacy board. Of the 4105 participants enrolled in IIDP, 3778 (92%) were identified in INPC using social security numbers, name, gender, and date of birth. For each individual, we retrieved serum glucose and hemoglobin A1c measures associated with outpatient visits, *International Classification of Diseases, Ninth Edition* (ICD-9), codes for diabetes and common comorbidities, and the use of diabetes medications classified as insulin only, oral antidiabetic medication only, or both insulin and oral medications. In addition, ICD-9 codes were used in the EMR to define diabetes complications [19].

3. Statistical analyses

Because our analysis is focused on the change in glucose levels, repeated glucose measures were used as the outcome variables. Three groups of participants were defined in the analysis. The first group consisted of participants with incident dementia diagnosed at or after the 1995 evaluation for those in the original cohort and after the 2001 evaluation for participants enrolled in 2001. A second group consisted of participants diagnosed with MCI at their last evaluation. The third group consisted of participants who were either diagnosed as normal or were determined to have good cognitive function at their last follow-up evaluation. Because we are interested in the within-person changes in glucose levels before dementia diagnosis, only participants with at least two glucose measures before reaching IIDP study endpoints are included in this analysis. Participants with one or no glucose measure or those diagnosed with dementia before their first glucose measures were excluded from the analysis. This analysis included 1991 participants with longitudinal glucose values who contributed a total of 22,865 glucose measures, where the glucose values were daily averaged glucose values, and 1630 of the glucose values were calculated from hemoglobin A1c values ($28.7 \times$ hemoglobin A1C $- 46.7$) as done in previous studies [11].

To compare changes in serum glucose levels before the clinical diagnosis of dementia or MCI to those in normal participants, we aligned the timing of the glucose measurements to an index time point defined to be the time of diagnosis for participants with incident dementia and the time of last evaluation for normal participants. As participants with MCI in our cohort have heterogeneous outcomes, we included only those who were diagnosed with MCI at their last evaluation in the MCI category allowing those whose diagnosis had changed to normal or dementia to be included in the respective categories. Therefore, glucose measures taken during the course of the study were aligned by the number of years serum glucose was measured before the index time. In all our statistical models, index time was coded as time zero. For example, a participant with serum glucose measured at 1995 and a diagnosis of dementia in 2007 would have time coded as -12, indicating that glucose was measured 12 years before the dementia diagnosis.

Demographic characteristics and medical history among the three groups were compared using chi-square tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Covariates considered for the mixed effects models included baseline age, gender, years of education, alcohol, smoking, BMI, systolic and diastolic pressure, history of hypertension, coronary heart disease,