ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring ■ (2017) 1-5

Alzheimer's & Dementia

Cerebrospinal Fluid Biomarkers

Type 2 diabetes mellitus and cerebrospinal fluid Alzheimer's disease biomarker Aβ1-42 in Alzheimer's Disease Neuroimaging Initiative participants

Wei Li[a,*], Shannon L. Risacher[b], Sujuan Gao[c], Stephen L. Boehm II[d], Jeffrey S. Elmendorf[e,f], Andrew J. Saykin[b], for the Alzheimer's Disease Neuroimaging Initiative[1]

[a]Physician Assistant Studies, School of Health Professions, University of Alabama at Birmingham, Birmingham, AL, USA
[b]Department of Radiology and Imaging Sciences, Center for Neuroimaging, Indiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, IN, USA
[c]Department of Biostatistics, Indiana University School of Medicine, Indianapolis, IN, USA
[d]Department of Psychology, School of Science, Indiana University-Purdue University Indianapolis, Indianapolis, IN, USA
[e]Department of Cellular and Integrative Physiology, Center for Diabetes and Metabolic Diseases, Indiana University School of Medicine, Indianapolis, IN, USA
[f]Department of Biochemistry and Molecular Biology, Center for Diabetes and Metabolic Diseases, Indiana University School of Medicine, Indianapolis, IN, USA

Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a risk factor for Alzheimer's disease. Cerebrospinal fluid (CSF) β amyloid (Aβ) 1-42 is an important Alzheimer's disease biomarker. However, it is inconclusive on how T2DM is related to CSF Aβ1-42.

Methods: Participants with T2DM were selected from the Alzheimer's Disease Neuroimaging Initiative by searching keywords from the medical history database. A two-way analysis of covariance model was used to analyze how T2DM associates with CSF Aβ1-42 or cerebral cortical Aβ.

Results: CSF Aβ1-42 was higher in the T2DM group than the nondiabetic group. The inverse relation between CSF Aβ1-42 and cerebral cortical Aβ was independent of T2DM status. Participants with T2DM had a lower cerebral cortical Aβ in anterior cingulate, precuneus, and temporal lobe than controls.

Discussion: T2DM is positively associated with CSF Aβ1-42 but negatively with cerebral cortical Aβ. The decreased cerebral cortical Aβ associated with T2DM is preferentially located in certain brain regions.

Keywords: Amyloid β; Aβ1-42; Alzheimer's disease; Cerebrospinal fluid (CSF); Type 2 diabetes mellitus

1. Introduction

In 1999, the Rotterdam Study found that type 2 diabetes mellitus (T2DM) could double the risk of Alzheimer's disease (AD) [1]. In 2011, another study reported that AD risk increased 60% in patients with T2DM over the nondiabetics [2]. Further, a high prevalence of T2DM in patients with AD is congruent with T2DM as an AD risk factor [3]. Cerebrospinal fluid (CSF) β amyloid (Aβ) 1-42 has been shown as a sensitive biomarker for diagnosing AD [4] and

On behalf of all authors, the corresponding author states that there is no conflict of interest.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp- content/uploads/how_to_apply/ADNI_Acknowledgement_ List.pdf.

*Corresponding author. Tel.: +(205)-996-2656; Fax: +205-975-7302.
E-mail address: wli@uab.edu

https://doi.org/10.1016/j.dadm.2017.11.002

a strong predictor for people with subjective cognitive complaints to progress to AD [5]. However, a recent study did not find the association between T2DM and CSF Aβ1-42 [6]. Using data from participants enrolled in Alzheimer's Disease Neuroimaging Initiative (ADNI), we investigated the relationship between CSF Aβ1-42 with T2DM and baseline cognition diagnosis. Aβ load in cerebral cortex as well as its subregions was also compared between participants with and without T2DM. Our findings provide important insight into CSF Aβ1-42 as an AD biomarker and its relation to the cerebral cortical Aβ, especially for patients with T2DM.

2. Methods

2.1. ADNI

Demographic and imaging data were downloaded from the ADNI database (adni.loni.usc.edu). As an ongoing project, ADNI was launched in 2003 and has been sponsored by the following agencies: National Institute on Aging, National Institute of Biomedical Imaging and Bioengineering, Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. The primary goal of the ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography (PET), biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. In three phases (1, GO, and 2) and from over 50 sites across the United States and Canada, the ADNI has recruited more than 1800 adult participants. The participants are older adults (aged 55–90 years) with normal cognition, MCI, or mild AD. Further information can be found at http://www.adni-info.org/ and in previous reports [7–12].

2.2. Selection of T2DM participants

The following search terms were used in the medical history database to screen the ADNI participants: diabetes, diabetic, and insulin. Based on the medical history information (age at onset of diabetes, clinical diagnosis, and/or use of diabetic medications), 159 participants from the ADNI were found to have T2DM at the screening visit (Table 1). In these diabetic participants, 76.73% (122/159) were being treated with antidiabetic medications. These diabetic participants had an average fasting glucose level between 110 and 120 mg/dL at the baseline and at 12-, 24-, and 36-month follow-up visits.

2.3. CSF Aβ1-42 measures

CSF samples were collected by following standard procedures stated in the ADNI protocols. AD biomarkers including Aβ1-42 were measured at the ADNI Biomarkers Core located at the University of Pennsylvania. In brief, all CSF samples were collected from the participants after at least a 6-hour fasting period. The CSF samples were analyzed by following storing, shipping, and testing procedures and with parallel strict quality control steps. To date, eight batches of data on CSF biomarkers have been released from the Biomarkers Core. Only baseline CSF Aβ1-42 and corresponding cerebral cortical Aβ PET measures were being analyzed in the present study.

2.4. ^{18}F florbetapir AV45 PET imaging and analysis

Preprocessed florbetapir imaging data were downloaded from the LONI ADNI site (http://adni.loni.usc.edu). Data preprocessing information is available online (adni.loni.ucla.edu/about-data-samples/image-data/). Briefly, image data were acquired in four 5-min frames 50–70 minutes after injection of approximately 10 mCi of ^{18}F florbetapir, the four frames were co-registered to one another, averaged, interpolated to a uniform image and voxel size ($160 \times 106 \times 96$, 1.5 mm^3), and smoothed to a uniform resolution (8 mm FWHM) to account for differences between scanners [13].

For quantifying cerebral cortical Aβ, preprocessed florbetapir image data and co-registered structural magnetic resonance images were analyzed using Freesurfer software, version 4.5.0 (surfer.nmr.mgh.harvard.edu/) as described before [14] and online (adni.loni.ucla.edu/research/pet-post-processing/). The mean Aβ retention, measured by the florbetapir AV45 standardized uptake value ratio, was normalized to the whole cerebellum as a summary measure of florbetapir retention for each participant.

Table 1
Participant demographics and clinical information

	T2DM	Nondiabetics
N	77	735
Age (<75:75–80:>80)	53 (68.83%):18 (23.38%):6 (7.80%)	454 (61.77%):179 (24.35%):102 (13.88%)
(Mean ± SD)	(70.48 ± 6.71)	(72.17 ± 7.37)
Gender (M: F)	46:31	384:351
APOE e4 carrier status (+/−)	39:37	327:404
APOE genotype (e2e2: e2e3: e3e3: e2e4: e3e4: e4e4)	0 (0%):4 (5.19%):33 (42.86%):1 (1.30%): 32 (41.56%):6 (7.80%)	1 (0.14%):59(8.03%):344 (46.80%):9 (1.22%): 245 (33.33%):73 (9.93%)
Education	15.74 ± 2.44	16.31 ± 2.62
HC: MCI: AD	10:54:2	151:493:7

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein epsilon; HC, healthy control; MCI, mild cognitive impairment; T2DM, type 2 diabetes mellitus; SD, standard deviation.