Is diabetes associated with increased pathological burden in Alzheimer’s disease?

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Abstract

Introduction: We examined the association between Alzheimer’s disease (AD) and type 2 diabetes mellitus (DM) and hypothesized that diabetes is associated with an increased pathological burden in clinically and pathologically diagnosed AD.

Methods: All data were obtained from the Uniform Data Set (UDS) v3, the Neuropathology Data Set, and the Researcher’s Data Dictionary-Genetic Data from the National Alzheimer’s Coordinating Center. The dataset (37 cases with diabetes and 1158 cases without) relies on autopsy-confirmed data in clinically diagnosed AD patients who were assessed for diabetes type in form A5 or D2 during at least one visit. Differences in scores were explored using a general linear model. Effect sizes were calculated using sample means and standard deviations (Cohen’s $d$).

Results: The presence of diabetes was associated with a lower Thal phase of amyloid plaques (A score; $4.6 \pm 0.79$ vs. $4.3 \pm 0.85$, $P < .05$) and lower Braak stage for neurofibrillary degeneration (B score; $5.58 \pm 0.72$ vs. $5.16 \pm 0.96$, $P < 0.05$) but not for density of neocortical neuritic plaques (CERAD score-C score). The National Institute on Aging–Alzheimer’s Association Alzheimer’s disease neuropathologic change (ABC score) was not different between AD+DM and AD-DM.

Discussion: This pilot study found a significantly lower Thal phase of amyloid plaques and Braak stage for neurofibrillary degeneration in AD-confirmed individuals with diabetes compared to those without. Thus type 2 DM is not associated with increased AD pathology in clinically and pathologically confirmed cases of AD.

KEYWORDS
Alzheimer’s disease, Alzheimer’s disease neuropathologic change (ABC score), Braak neurofibrillary stage (B score), neuritic plaque score (C score), Thal phase (A score), type 2 diabetes mellitus
Alzheimer’s disease (AD) is a progressive and irreversible neurodegenerative disorder pathologically defined by the presence of neurofibrillary tangles (NFTs) in the brain as well as senile plaques that primarily consist of amyloid beta (Aβ) peptides.1 Type 2 diabetes mellitus (T2DM), which is also pervasive among aging populations, is characterized by insufficient insulin secretion by the pancreas and insulin resistance.2 Although these two diseases are often linked at the epidemiological and clinical levels, a solid molecular connection explaining this relationship has yet to be established.3,4 Our study set the epidemiological and clinical levels, a solid molecular connection explaining this relationship has yet to be established.3,4 Our study set out to supply compelling evidence that provides a tangible, pathophysiological link between two devastating chronic diseases that negatively impact the lives of millions worldwide.

Studies have investigated the relationship between T2DM and AD at the pathophysiological level, specifically whether T2DM catalyzes the onset of AD, but the literature is inconclusive. For example, Heitner and Dickson could not demonstrate a neuropathological connection between diabetes and AD;5 whereas Beeri et al. reported that individuals with T2DM had less AD neuropathology than non-diabetics.6 Some studies have failed to discover an association between T2DM and AD pathogenesis altogether and instead found a relationship between diabetes and cerebrovascular pathology.7–11 Matsuizaki et al., however, revealed a positive association between biological irregularities associated with T2DM and the acceleration of senile plaque formation.12 The breadth of inconsistency surrounding this controversial topic indicates that further exploration is both needed and warranted. Further, no previous study has used the dataset from the National Alzheimer’s Coordinating Center.

Research indicates that T2DM and AD share several pathophysiological mechanisms.13 Insulin resistance has been identified as a critical mechanistic link between the two diseases.14 Peripheral insulin resistance, a staple of the T2DM pathology, generates a hyperglycemic microenvironment within the body, as well as a state of chronic hyperinsulinemia.15 Perpetually elevated peripheral insulin levels downregulate insulin receptors found at the blood-brain barrier, which creates a hypoglycemic microenvironment within the brain.16 GLUT4, in particular, is an insulin-sensitive glucose transporter abundant in this region that increases glucose uptake into the brain. The downregulation of this transporter and other insulin receptors decreases neural glucose metabolism, reduces the presence of neural insulin, and establishes a state of central insulin resistance.17 Insulin-degrading enzyme (IDE) is responsible for insulin degradation, but it is also a key Aβ-degrading enzyme found within the brain.18 This enzyme has a much higher affinity for insulin than Aβ, so the surplus of peripheral insulin generated by insulin resistance competitively inhibits IDE and decreases the level of Aβ clearance in the brain.19 Intact Aβ peptides aggregate into senile plaques and also interact with tau protein signaling pathways that promote tau hyperphosphorylation and cause NFT formation within neurons, which exacerbates the AD pathology.20

It has been suggested that T2DM and AD may share pathogenic mechanisms that similarly impact cognition and are downstream from amyloid in AD, such as increased inflammation and oxidative stress, dyslipidemia, impaired mitochondrial and synaptic function, and impaired brain insulin signaling.21 These T2DM-related abnormalities can produce an AD clinical phenotype in the absence of amyloid. Understanding these associations is imperative for anti-amyloid treatment trials enrolling patients clinically diagnosed with AD and for other precision medicine approaches to prevent and treat AD and related disorders. Concerning tau, although neuropathological studies do not indicate increased NFT deposition in T2DM, several large studies have documented increased cerebrospinal fluid (CSF) tau.22 Co-localization of tangles and insulin resistance markers have also been reported in neuropathological studies of AD.23

The pathophysiological link between T2DM and AD is undeniable and deserves meticulous exploration. The purpose of the study was to examine the relationship between the diseases through biological mechanisms in which T2DM relates to and promotes AD pathology. This study tested the hypothesis that T2DM is associated with an increased pathological burden in clinically and pathologically diagnosed AD. Our findings do not confirm our hypothesis.

3. Future Directions: Further investigations are need to determine how T2DM affects AD pathologically and clinically.

2 | METHODS

2.1 Study sample

All data were obtained from the Uniform Data Set (UDS), the Neuropathology Data Set, and the Researcher’s Data Dictionary-Genetic Data from the National Alzheimer’s Coordinating Center (NACC), a

RESEARCH IN CONTEXT

1. Systematic Review: The authors did an extensive PubMed search to read and understand the literature that explores the connection between type 2 diabetes mellitus (DM) and Alzheimer’s disease (AD) pathology. To publish this paper, the content was submitted to the National Alzheimer’s Coordinating Center for review and approval because the data were acquired from the Alzheimer’s Disease Resource Center network.

2. Interpretation: The pathophysiological link between T2DM and AD is undeniable and deserves meticulous exploration. The purpose of the study was to examine the relationship between the diseases through biological mechanisms in which T2DM relates to and promotes AD pathology. This study tested the hypothesis that T2DM is associated with an increased pathological burden in clinically and pathologically diagnosed AD. Our findings do not confirm our hypothesis.

3. Future Directions: Further investigations are need to determine how T2DM affects AD pathologically and clinically.
The NACC’s data request website provided all of the data necessary for this study. The proposal posed in the query questioned whether T2DM is associated with an increased pathological burden in clinically and pathologically diagnosed AD dementia. To facilitate the acquisition of pertinent variables, the following keywords were used: “Alzheimer’s disease,” “type 2 diabetes mellitus,” “Thal phase (A score),” “Braak neurofibrillary stage (B score),” “Neuritic plaque score (C score),” and “Alzheimer’s disease neuropathology change (ABC score).” The start date of the UDS (September 2005) was used, and the data freeze includes data up to June 2019.

AD participants who came to autopsy were assessed based on their diabetic status (absent or recent/active). Participants were placed in either the DM status absent or recent/active group. Differences in A, B, and C scores, as well as the composite ABC score, were explored between subjects with and without T2DM using one-way analysis of variance (ANOVA).

### 2.2 Analyses

Sample descriptive statistics were calculated as a function of DM status for age, education, sex, and race. Differences in demographics were explored between groups using ANOVA for continuous variables and Chi-square for categorical variables. Differences in AD pathology were explored via separate one-way ANOVA using A, B, and C scores, and composite pathology scores (e.g., ABC Score) as dependent variables and DM status as the independent variable. Any demographic variables differing between groups were entered as covariates. A generalized linear model, which models data based on any distribution, was used to explore differences in scores. As such, response variables were not normalized and instead derived from an exponential distribution. Cohen’s d was also calculated as a measure of effect size.

### 3 RESULTS

The demographic composition of the subjects analyzed is shown in Table 1. A total of 1195 subjects had pathology-confirmed AD, completed a baseline visit, and had a known diabetes status. Of this sample, 3.1% had active T2DM. For AD-confirmed individuals with T2DM, the mean age was 75.7 ± 10.3 years. Mean years of education was 15.6 ± 4.0; 32.4% of the subjects were female. For AD-confirmed individuals without T2DM, the mean age at baseline was 73.5 ± 10.3 years, and the mean years of education for the group were 15.4 ± 3.0; 50.3% of the subjects were female.

The mean scores at different pathology stages for AD-confirmed individuals with T2DM and AD-confirmed individuals without T2DM are displayed in Table 2. Individuals with pathology-confirmed AD and T2DM had a significantly lower Braak stage for neurofibrillary degeneration (F [1, 1193] = 11.79, P = .001) and a significantly lower Thal phase of amyloid plaques (F [1, 1193] = 5.34, P = .021). Recent or active
TABLE 1  Demographics by diabetic status

| Demographic data by group | DM status  | N  | Mean | Std. deviation |
|---------------------------|------------|----|------|----------------|
| Age (years)               | Absent     | 1158 | 73.5 | 10.3           |
|                           | Recent/active | 37  | 75.7 | 6.7            |
| Education (years)         | Absent     | 1146 | 15.4 | 3.0            |
|                           | Recent/active | 37  | 15.6 | 4.0            |
| Sex (% female)            | Absent     | 50.3% | —    | —              |
|                           | Recent/active | 32.4% | —    | —              |
| Race (% non-White)        | Absent     | 7.0%  | —    | —              |
|                           | Recent/active | 16.2% | —    | —              |

Abbreviation: DM, diabetes mellitus.
* = P < .05

TABLE 2  Descriptive statistics for pathology staging by group

| DM status  | N  | Mean | Std. deviation |
|------------|----|------|----------------|
| Thal phase for amyloid plaques (A score)* | Absent | 1158 | 4.60 | 0.790 |
|           | Recent/active | 37  | 4.30 | 0.845 |
| Braak stage for neurofibrillary degeneration (B score)* | Absent | 1158 | 5.58 | 0.718 |
|           | Recent/active | 37  | 5.16 | 0.958 |
| Density of neocortical neuritic plaques (CERAD score; C score) | Absent | 1158 | 2.79 | 0.407 |
|           | Recent/active | 37  | 2.78 | 0.417 |
| NIA-AA Alzheimer’s disease neuropathologic change (ADNC; ABC score) | Absent | 1158 | 2.90 | 0.549 |
|           | Recent/active | 37  | 2.73 | 0.450 |
| Density of diffuse plaques (CERAD semiquantitative score) | Absent | 1158 | 3.03 | 1.165 |
|           | Recent/active | 37  | 3.27 | 1.465 |

Abbreviations: AA, Alzheimer’s Association; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DM, diabetes mellitus; NIA, National Institute on Aging.
* = P < .05

T2DM was also associated with a lower NIA–Alzheimer’s Association (NIA-AA) Alzheimer’s disease neuropathologic change (ADNC) score. However, the difference was not statistically significant. Individuals with pathology-confirmed AD and T2DM also had a slightly higher density of diffuse plaques than AD-confirmed individuals without T2DM, though the difference was not significant (F [1, 1193] = 1.54, P = .215). Individuals with pathology-confirmed AD and T2DM did not differ in density of neocortical neuritic plaques from those without T2DM (F [1, 1193] = .01, P = .92).

4 | DISCUSSION

This study tested the hypothesis that T2DM is associated with an increased pathological burden in clinically and pathologically diagnosed AD. Based on the analysis of the dataset we obtained from the NACC and assessment of the differences in pathology staging between AD-confirmed individuals with T2DM and those without an AD confirmation, numerous key findings were identified. Contrary to our hypotheses, we found that the presence of T2DM is not associated with increased AD pathology in clinically and pathologically confirmed cases of AD. Instead, recent or active T2DM was associated with a lower Thal phase of amyloid plaques. The presence of T2DM was also associated with a lower Braak stage for neurofibrillary degeneration. AD-confirmed individuals with T2DM were found to have no difference in the density of neocortical neuritic or diffuse plaques. Collectively, these data suggest that there is no increased amyloid burden in AD individuals with T2DM than without T2DM.

Evidence supporting the notion that T2DM catalyzes AD pathogenesis is appealing from a molecular standpoint. A critical enzyme involved in blood glucose regulation is glycogen synthase kinase-3β (GSK-3β), and it is regulated by insulin in the phosphoinositol-3-kinase/Akt signaling pathway.26 Individuals with T2DM overexpress GSK-3β: excessive activation of this enzyme causes signaling pathway impairment that creates a hyperglycemic microenvironment and insulin resistance.27 The overexpression of GSK-3β also contributes to tau protein hyperphosphorylation, which is involved in accelerating AD neuropathology.28 Hyperglycemia has been implicated in the
formation of reactive oxygen species (ROS), and research suggests that T2DM depletes cellular antioxidant systems found within the body.29 These conditions establish endogenous oxidative stress, which has a deleterious impact on many biological systems, leads to mitochondrial dysfunction, and catalyzes both Aβ production and aggregation in the brain.30 Chronic hyperglycemia and oxidative stress work synergistically to amplify the production of advanced glycation end-products (AGEs) in individuals with T2DM.31 AGEs, which are also found within Aβ-plaques and NFTs, accelerate Aβ deposition in the brain through their attachment to multi-ligand receptors called RAGE. Activation of RAGE receptors stimulates the expression of an enzyme needed for Aβ production (i.e., β-site amyloid precursor-cleaving enzyme 1 [BACE1]) and facilitates the migration of circulating Aβ peptides into the brain.32,33 RAGE receptor activation also generates ROS and inflammatory responses intended to counteract the reactive species, which creates a perpetuating cycle of increased AGE production and subsequent inflammation.34 Valente et al. observed that post mortem brain samples exhibiting T2DM, and AD showed increased amounts of AGEs, RAGEs, and Aβ plaques compared to brains that only displayed AD.35

Many studies do not support a relationship between T2DM and increased AD pathology, and our report concurs with these findings. Overall, rigorous neuropathological studies have shown that insulin resistance, pre-diabetes, and T2DM are not associated with amyloid load or that amyloid load is unaffected by diabetic status in adults with mild cognitive impairment or AD.30 This lack of association is likely impacted by differences in methodology and research design.36 Pruzin et al. could not demonstrate a connection between diabetes and AD neuropathology at either regional or global levels.37 Their investigation was designed as a longitudinal cohort study that enrolled non-representative of individuals in the general community, the interpretability of these data is compromised and subjected to selection bias. Future studies should consider the impact of genes associated with the T2DM pathology that may provide valuable insights regarding the enhanced production of Aβ plaques. The APOE ε4 allele, specifically, has been identified by many studies as a critical associative factor between T2DM and AD.12,38,39,41,42 Luchsinger et al. demonstrate the strong predictive relationship between APOE ε4 genotype and Aβ burden; carriers of the allele were more likely to possess intermediate and high levels of Aβ compared to non-carriers.43 Future treatments for individuals with T2DM should target physiological processes implicated in increased Aβ generation within the brain. As a result, the progression of the AD pathology may be hindered or stopped altogether. Future investigations should also explore deposition patterns through various neuroimaging techniques; the visualization of the neuropathological hallmarks of AD may provide insight as to how T2DM affects AD pathogenesis or its progression within different parts of the brain. Takenoshita et al. relied on positron emission technology to identify clinically diagnosed AD patients with T2DM with neuronal damage devoid of Aβ neurotoxicity.44 The neuronal damage and
subsequent dementia were instead attributed to a suspected form of pure tauopathy.\textsuperscript{44} Identifying aberrant brain imaging patterns through neuroimaging will be significant for the future of clinical practice when considering T2DM, AD, and the interaction between the two diseases because it affects diagnoses, treatment methods, and overall patient care. Taken together, this body of work suggests that many adults with T2DM express AD-like symptoms at lower levels of amyloid burden, perhaps due to the added impact of vascular or tau abnormalities in midlife; however, AD pathology appears to be potentiated by T2DM-related factors such as insulin resistance.

More extensive research needs to be performed on this complex and multifactorial relationship to provide conclusive answers that explain their connection and elucidate improved understandings of these permissive conditions; through this needed exploration, future preventive methods and treatment, as well as health-care delivery, can be revolutionized to better serve the needs of patient populations across the world.

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\section*{Conflicts of Interest}

Kaviyon Sadrolashrifi has nothing to disclose. Dr. Craft discloses he is PI and director of the Wake Forest ADRC (P30 AG072947) and has grant support from U24 AG 057437, R01 AG055122, R01 AG058969, R01 AG054523, R01 AG054069, R01 AG058829, U19 AG063744, R03 AG 063299, R01 AG053798, R01 AG062624, R01 AG057725, R01 AG064014, R91 AG070883. She receives consulting fees from Roche, Biogen, Cortexyme, vTv Therapeutics, Renew Research, Cognito Therapeutics, T3D, and Philips Healthworks. She receives honoraria from PER, Knapp, and Medscape. She discloses one patent. Dr. Decourt discloses grant support from NIH P20 AG 068053, R01AG59003, K01 AG047279. Dr. Adem has nothing to disclose. Dr. Wilson has nothing to disclose. Dr. Miller receives grant support from NIH P20 AG 068053 and P20 GM109025. Dr. Sabbagh discloses grant support from NIH P20 AG 068053, P20 AG109025, R01 059008; ownership interest (stock or stock options): Brain Health Inc, NeuroTau, Optimal Cognitive Health Company, uMethod Health, Versanum, Athira, Cognitopia; consulting: Alzheon, Biogen, Cortexyme, Roche-Genentech, Stage 2 Innovations/Renew Research, Acadia, T3D, Eisai, KefleRx; royalties: HarperCollins, Humanix.

\section*{Author Contributions}

Kaviyon Sadrolashrifi assisted in data acquisition and analysis and drafted a significant portion of the manuscript. Justin Miller assisted in data acquisition and analysis. Suzanne Craft drafted a significant portion of the manuscript, Boris Decourt drafted a significant portion of the manuscript, Abdu Adem drafted a significant portion of the manuscript. Jeffrey R. Wilson assisted in analysis, and Marwan N. Sabbagh conceived of the project and assisted in data acquisition and analysis and the drafting of the manuscript.

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