Importance of Treatment Status in Links Between Type 2 Diabetes and Alzheimer Disease

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OBJECTIVE

To investigate relationships among type 2 diabetes treatment, Alzheimer disease biomarkers, and risk for dementia.

RESEARCH DESIGN AND METHODS

Participants from the Alzheimer Disease Neuroimaging Initiative (*N* = 1,289) who were dementia-free at baseline and underwent health assessment, cognitive testing, and MRI. A subset (*n* = 900) obtained a lumbar puncture to determine cerebrospinal fluid (CSF) phosphorylated tau (p-tau), total tau (t-tau), and β-amyloid 1-42 (Aβ1-42). Participants were grouped by fasting blood glucose and medication history: euglycemia (EU), prediabetes (PD), untreated diabetes (UD), and treated diabetes (TD). Relationships were investigated between treatment status and CSF biomarkers and risk for dementia.

RESULTS

The UD group displayed greater p-tau, t-tau, and p-tau/Aβ1-42 levels than the EU, PD, and TD groups (*P* values <0.05) and higher t-tau/Aβ1-42 than the EU and PD groups (*P* values <0.05). The UD group progressed to dementia at higher rates than the EU group (hazard ratio 1.602 [95% CI 1.057–2.429]; *P* = 0.026).

CONCLUSIONS

Treatment status may alter the relationship between type 2 diabetes and both Alzheimer disease biomarker profile and risk for dementia. UD is associated with elevated tau pathology and risk for dementia, whereas TD is not. Although this study is observational and therefore causality cannot be inferred, findings support the potential importance of treatment status in Alzheimer disease risk associated with type 2 diabetes.

Epidemiological studies have repeatedly demonstrated associations between type 2 diabetes and Alzheimer disease (AD) and dementia (1). Although some studies have shown only weak links between type 2 diabetes and AD (2), others have found stronger associations between type 2 diabetes and vascular dementia (3). Type 2 diabetes in midlife, rather than late life, is more consistently associated with late-life AD. A large retrospective study showed the adjusted rate ratio for AD among patients with type 2 diabetes aged 70–79 years was 1.00 and decreased to 0.87 in patients aged 80 and older. In contrast, the adjusted rate ratios for AD in adults with type 2 diabetes aged 40–49 and 50–59 years were 1.55. and 1.62, respectively (3). Despite mixed findings concerning the relationship between type 2 diabetes and AD, it is widely agreed that type 2 diabetes is associated with worse cognition in multiple domains. Relative to

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people without diabetes, individuals with type 2 diabetes tend to perform worse on verbal memory, information processing speed and attention, and executive functioning (4), but the mechanism underlying this relationship is poorly understood.

Autopsy studies have often failed to find a significant association between type 2 diabetes and amyloid plaque and neurofibrillary tangle burden, whereas relationships between type 2 diabetes and cerebral infarcts at autopsy are more consistent (5). Inconsistent findings relating type 2 diabetes to AD neuropathology may be partly explained by the use of heterogeneous groups with type 2 diabetes and not accounting for the role of glycemic control. Population-based longitudinal studies show undiagnosed diabetes increases risk for dementia and AD relative to individuals with well-managed diabetes and without diabetes (6,7). Further, individuals with well-managed diabetes had similar rates of mortality and dementia to those without diabetes (6). Other longitudinal studies showed oral hypoglycemic medications for type 2 diabetes reduced cognitive decline or risk for dementia (8). These studies suggest diabetes treatment may mitigate dementia risk.

It is unclear whether the treatment of diabetes decreases risk for dementia through improvements in glycemic control, through other potential neuroprotective effects of diabetes medications, or both. In the ACCORD-MIND trial, baseline HbA_{1c} was negatively associated with cognitive performance on all four cognitive tests, demonstrating a relationship between diabetes severity and cognition (9). Several clinical trials have also shown cognitive benefits of improved glycemic control (10). There is less evidence for beneficial cognitive effects of intensive glucose lowering versus standard treatment. The ACCORD-MIND and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trials both failed to show any differences in cognition between those treated with intensive versus standard therapy (11,12). Some investigators have suggested that overly aggressive treatment may increase risk for episodes of hypoglycemia, potentially exacerbating cognitive decline and dementia risk (13). This was exemplified in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial in which participants in the insulin intervention arm had greater rates of nonsevere and severe hypoglycemia relative to those with standard treatment. Further, participants with mild cognitive impairment (MCI) were at greater risk for severe hypoglycemia (14).

Although several intervention studies using standard treatment with multiple drug classes have shown positive effects on cognition, there is an absence of large-scale randomized trials demonstrating these effects. Metformin, a first-line drug used to treat diabetes, decreased risk of dementia compared with nonusers (15,16), but one large study reported long-term use of metformin slightly increased risk of dementia (17). Animal research indicates metformin crosses the blood–brain barrier and may exert neuroprotective effects by attenuating tau phosphorylation (18). Peroxisome proliferator–activated receptor-γ agonists, including thiazolidinediones, also reduce amyloid plaque burden and inflammation in animal models (19) and may protect against cognitive decline in humans (20). Glucagon-like peptide 1 (GLP-1) agonists decrease neuronal loss, amyloid plaques, tau phosphorylation, and inflammation (21). Sulfonylureas medications can improve cognition and decrease dementia risk (15), but may convey greater hypoglycemia risk in dementia compared with insulin analogs (22). Lastly, research on whether systemic insulin is neuroprotective is mixed, and insulin therapy has been shown to increase dementia risk in population-based studies (23). The results are difficult to interpret given that patients using insulin usually have longer disease duration. Taken together, both animal and human studies suggest that several types of diabetes medications may be neuroprotective and thereby benefit cognitive function.

A recent study found that older adults with type 2 diabetes exhibited greater cerebrospinal fluid (CSF) phosphorylated tau (p-tau) and total tau (t-tau) (24), suggesting a link between hyperglycemia and tau-mediated neurodegeneration. Importantly, these findings were correlational, and it remains unclear whether improvement of glycemic control or neuroprotective effects of pharmacological treatment may attenuate the association with tau pathology. To our knowledge, the effects of type 2 diabetes treatment status on CSF AD biomarkers have never been investigated. Further research linking type 2 diabetes and in vivo biomarkers of AD pathophysiology in the context of treatment may provide additional insights into potential mechanisms relating these two diseases.

Diabetes treatment status has multiple determinants, including adherence, cognitive status, psychological status, and socioeconomic status. Thus, the effect of diabetes treatment on AD can only be determined by clinical trials. Observational studies can, however, evaluate the relationship between treatment status and AD-related outcomes. We conducted an observational study investigating whether treatment status modifies the relationship between type 2 diabetes and AD pathophysiology and dementia. The current study differentiated among individuals with euglycemia (EU), prediabetes (PD), untreated diabetes (UD), and treated diabetes (TD). We hypothesized that older adults with UD would have worse AD tau pathology relative to adults with normal blood glucose (EU) and PD. Further, we examined differential progression to dementia among groups over 120 months.

RESEARCH DESIGN AND METHODS

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The primary purpose of ADNI is to investigate the utility of MRI, positron emission tomography, CSF, and clinical, neuropsychological, and other biological markers in predicting progression of MCI to early AD dementia (25). For up-to-date information, see www.adni-info.org. Exclusion criteria from the ADNI study included a Hachinski ischemic score greater than four, inability to participate in MRI, presence of neurologic disorders, current depression, history of psychiatric diagnosis, recent substance dependence, $<$6 years of education, and lack of fluency in English or Spanish.

Participants

Participants were 1,289 nondemented ADNI-1, ADNI-Grand Opportunity (ADNI-GO), and ADNI-2 participants with fasting blood glucose data and/or evidence of type 2 diabetes medication use who were classified as cognitively normal or MCI

at screening evaluation (26). Participants were grouped by baseline fasting blood glucose and reported medications taken in the last 3 months. EU versus PD versus diabetes classification used guidelines recommended by the American Diabetes Association (27). The EU group (n = 762) had fasting blood glucose $<$100 mg/dL, the PD group (n = 353) had fasting blood glucose 100–125 mg/dL, and the UD group (n = 78) had fasting blood glucose $\geq$126 mg/dL. The EU, PD, and UD groups did not report type 2 diabetes medications. The TD group (n = 96) reported use of one or more type 2 diabetes medication. Demographic and clinical data are shown in Table 1. For the TD group, diabetes medications, diabetes complications, and time since diabetes diagnosis were recorded (Table 2). The number of participants who began treatment for type 2 diabetes over follow-up was noted (n = 9).

Genetic Data

Apolipoprotein E-ε4 (APOE-ε4) carrier status was determined using blood samples (99.4% of sample). Genotyping was conducted by the ADNI Biomarker Core at the University of Pennsylvania. Participants were designated as APOE-ε4 positive if they carried one or more APOE-ε4 alleles.

Vascular Risk Factors

Vascular risk factors were determined with physical examinations and clinical interviews at the start of study. Seated brachial artery blood pressure, weight, and height were measured. BMI was calculated as weight (kilograms) divided by height (meters) squared. Data on blood pressure and BMI were available for 99.7% of the sample. Fasted blood samples were used to measure fasting blood glucose (99.9% of sample). Diagnosis and treatment history for hypertension and diagnoses of dyslipidemia and cardiovascular disease were documented via interviews.

Depressive symptoms were measured using the Geriatric Depression Scale (GDS). Current depression, as defined by GDS $>$6, was an exclusion criterion.

Global Cognition and Risk for Dementia

Global cognition was measured using the Mini-Mental State Examination (MMSE). Dementia staging was measured using the Clinical Dementia Rating Sum of Boxes. Participants were diagnosed as normal, MCI, or AD at each follow-up visit. Participants were followed up to 120 months.

CSF Biomarkers

Baseline CSF biomarkers were collected and analyzed using Roche Elecsys CSF immunoassays for β-amyloid 1-42 (Aβ1-42), p-tau, and t-tau (picograms per milliliter) following Roche Study Protocol at the University of Pennsylvania/ADNI Biomarker Laboratory (28). Data on Aβ1-42 were available for 57.4% of the sample. Data on p-tau and t-tau were available for 69.8% and 69.9% of the sample, respectively. Based on previous studies, positive biomarker profiles were determined using the following cutoff values: Aβ1-42 ($<$964 pg/mL) and p-tau ($>$23.2 pg/mL) (29).

Statistical Analyses

All raw data were screened for departures from normality (skewness or kurtosis). Due to significant departures from the normal distribution, the following variables were log-transformed: p-tau, t-tau, and Aβ1-42. ADNI criteria for MCI have been criticized for high false-positive rates (30); thus, cognitively normal participants and participants with MCI were analyzed together. ANOVA and χ^2 tests were used to test for group differences in demographic, physiological, clinical, global cognition, dementia staging measures, and vascular risk factors.

Table 1—Clinical and demographic data

	All (N = 1,289)	EU (n = 762)	PD (n = 353)	UD (n = 78)	TD (n = 96)	F or χ^2	P value	Partial η^2 or ϕ
Baseline clinical/demographic data								
Age, years	73.54 (7.06)	73.32 (7.18)	73.84 (6.92)	75.04 (6.96)	72.87 (6.61)	1.927	0.123[a,b]	0.004
Sex (male), no. (%)	719 (55.8)	394 (51.7)	215 (60.9)	41 (52.6)	69 (71.9)	19.774	$<$0.001[c,d]	0.122
Education, years	16.04 (2.81)	16.08 (2.80)	16.08 (2.79)	15.86 (2.96)	15.72 (2.76)	0.603	0.613	0.001
Diagnosis (MCI), no. (%)	856 (66.3)	515 (67.6)	219 (62.0)	50 (64.1)	70 (72.9)	2.737	0.434[e]	0.065
APOE-ε4 (ε4 positive), no. (%)	546 (42.3)	331 (43.4)	144 (40.8)	33 (42.3)	37 (38.5)	2.271	0.518	0.030
MMSE	28.09 (1.76)	28.11 (1.75)	28.15 (1.75)	27.65 (1.97)	28.03 (1.67)	1.792	0.147[f]	0.004
CDR-SB	1.02 (1.00)	1.03 (1.01)	0.95 (0.98)	1.09 (1.14)	1.13 (0.93)	1.173	0.319	0.003
GDS	1.37 (1.39)	1.38 (1.40)	1.35 (1.37)	1.18 (1.40)	1.52 (1.40)	0.903	0.439	0.002
Baseline vascular risk factors								
Glucose	101.20 (24.32)	89.54 (7.24)	108.09 (6.85)	144.50 (16.70)	128.02 (46.87)	503.811	0.001[d,g,h]	0.541
BMI	27.03 (4.62)	26.53 (4.34)	27.37 (4.84)	26.84 (4.39)	29.80 (5.08)	15.618	0.001[c]	0.035
Systolic BP	134.34 (16.40)	133.63 (16.73)	135.26 (15.52)	137.01 (16.83)	134.41 (16.48)	1.536	0.204	0.004
Diastolic BP	74.33 (9.65)	74.37 (10.04)	74.60 (9.19)	73.63 (8.28)	73.66 (9.21)	0.386	0.763	0.001
HTN Tx, no. (%)	652 (50.6)	356 (46.7)	187 (53.0)	33 (42.3)	76 (79.2)	38.874	$<$0.001[c]	0.174
HTN, no. (%)	599 (46.4)	328 (43.0)	172 (48.7)	31 (39.7)	67 (69.8)	27.074	$<$0.001[c]	0.144
Dyslipidemia, no. (%)	606 (46.9)	328 (43.0)	177 (50.1)	33 (42.3)	67 (69.8)	27.266	$<$0.001[c,d]	0.144
CVD, no. (%)	87 (6.7)	45 (5.9)	22 (6.2)	5 (6.4)	14 (14.6)	10.487	0.015[h]	0.090

Data are mean (SD) unless otherwise indicated. BP, blood pressure; CDR-SB, Clinical Dementia Rating Sum of Boxes; CVD, cardiovascular disease; HTN, hypertension; Tx, treatment. [a]UD $>$ EU. [b]UD $>$ TD. [c]TD $>$ EU = PD = UD. [d]PD $>$ EU. [e]TD $>$ PD. [f]EU = PD $>$ UD. [g]UD $>$ EU = PD = TD. [h]TD $>$ EU = PD.

Table 2—Medications and complications data for TD group

Diabetes duration and medications	
Duration, years [mean (SD)]	9.97 (10.32)
Biguanides	62 (64.6)
SU	35 (36.5)
TZD	17 (17.7)
DPP-4 inhibitor	6 (6.3)
Insulin	10 (10.4)
GLP-1 agonist	1 (1.0)
Other	6 (6.3)
Diabetic complications	
Neuropathy	5 (5.21)
Retinopathy	2 (2.1)
Amputation	1 (1.0)
Skin issue	1 (1.0)

Data are number (%) unless otherwise indicated. DPP-4, dipeptidyl peptidase; SU, sulfonylurea; TZD, thiazolidinedione.

ANCOVA was used to assess group differences in CSF AD biomarkers. Pairwise comparisons were investigated using post hoc least significant difference tests. To assess group differences in p-tau and Aβ1-42 biomarker profiles, χ^2 analyses were employed using the cutoffs specified above and then confirmed with logistic regression analyses with covariates described below. In the TD group, linear regression was used to analyze relationship between diabetes duration and AD biomarkers. Cox regression investigated the relationship between baseline group status and progression to dementia using months to dementia diagnosis as the time variable covarying for baseline diagnosis. For ANCOVA, logistic regression, and Cox regression analyses, the following covariates were used: age, sex, years of education, APOE-ε4 carrier status, depression score, BMI, systolic and diastolic blood pressure, use of hypertension medication, dyslipidemia, and cardiovascular disease.

All analyses were two-tailed significance set at $P < 0.05$. Post hoc power analyses were conducted for CSF biomarker ANCOVA analyses using G*Power software. To address multiple comparisons for ANCOVA, χ^2, and logistic regression analyses, a 0.05 false discovery rate correction was applied (31). Analyses were performed with SPSS for Mac OS X version 24 (IBM Corporation).

RESULTS

Demographic and Clinical Data

Participant groups differed in sex ratio, BMI, and fasting glucose (P values <0.001) (Table 1). The TD group had more males than the EU ($P < 0.001$), PD ($P = 0.048$), and UD ($P = 0.009$) groups. The PD group had more males than the EU group ($P = 0.004$). The TD group had greater BMI than all groups (P values <0.001), and the EU group had lower BMI than the PD group ($P = 0.004$). The UD group had greater fasting blood glucose relative to all other groups (P values <0.001). The TD group had greater fasting blood glucose relative to the EU and PD groups (P values <0.001), and the PD group had greater glucose relative to the EU group ($P < 0.001$). Additionally, the UD group was older than the EU ($P = 0.041$) and TD ($P = 0.044$) groups.

The TD group was more likely to report use of antihypertensive medication, a history of hypertension and dyslipidemia relative to all groups (P values <0.01), and a history of cardiovascular disease relative to the EU and PD groups (P values <0.01). The PD group was more likely to report a history of dyslipidemia than the EU group ($P = 0.027$).

Nine participants in the nontreatment groups began treatment for type 2 diabetes over the course of follow-up (EU: $n = 2$, 0.26% of group; PD: $n = 4$, 1.13% of group; and UD: $n = 3$, 3.85% of group).

Global Cognition and Risk for Dementia

The TD group had greater rates of MCI than the PD group ($P = 0.048$), and the UD group scored worse on the MMSE than the EU ($P = 0.029$) and PD ($P = 0.025$) groups (Table 1). A total of 331 participants (26.8%) progressed to dementia over follow-up. On Cox regression analyses, UD participants showed more rapid progression to dementia compared with EU participants (hazard ratio 1.558 [95% CI 1.028–2.361]; $P = 0.037$). Further, this finding remained significant after excluding participants who began type 2 diabetes treatment after baseline ($n = 9$) (hazard ratio 1.602 [95% CI 1.057–2.429]; $P = 0.026$) (Fig. 1).

CSF Biomarkers

Table 3 provides summary statistics for group differences in CSF biomarkers and biomarker profiles. There were group differences in p-tau, t-tau, p-tau/Aβ1-42, t-tau/Aβ1-42, but not Aβ1-42. Specifically, the UD group exhibited greater p-tau than the EU ($P < 0.001$; Hedge $g = 0.57$), PD ($P = 0.001$; Hedge $g = 0.61$), and TD ($P = 0.025$; Hedge $g = 0.47$) groups. Similarly, the UD group had greater t-tau than the EU ($P < 0.001$; Hedge $g = 0.57$), PD ($P = 0.002$; Hedge $g = 0.60$), and TD ($P = 0.046$; Hedge $g = 0.45$) groups. Further, the UD group had greater p-tau/Aβ1-42 than the EU ($P = 0.001$; Hedge $g = 0.55$), PD ($P = 0.002$; Hedge $g = 0.59$), and TD ($P = 0.021$; Hedge $g = 0.65$) groups and greater t-tau/Aβ1-42 than the EU ($P = 0.007$; Hedge $g = 0.51$) and PD ($P = 0.008$; Hedge $g = 0.56$) groups. The UD group had marginally greater t-tau/Aβ1-42 ratio than the TD group ($P = 0.058$). Given concern about power, post hoc pairwise comparisons for Aβ1-42 with the UD group were also run: EU vs. UD: $P = 0.615$, Hedge $g = 0.12$; PD vs. UD: $P = 0.522$, Hedge $g = 0.17$; and TD vs. UD: $P = 0.319$, Hedge $g = 0.33$.

χ^2 analyses showed group differences in p-tau profiles. Specifically, the UD group had more p-tau$^+$ individuals than the EU ($\chi^2 = 8.202$, $P = 0.004$, $\phi = 0.119$), PD ($\chi^2 = 9.997$, $P = 0.002$, $\phi = 0.182$), and TD ($\chi^2 = 5.035$, $P = 0.025$, $\phi = 0.204$) groups. Further, the UD group had more p-tau$^+$/ Aβ1-42$^+$ individuals than the EU ($\chi^2 = 6.045$, $P = 0.014$, $\phi = 0.112$), PD ($\chi^2 = 7.602$, $P = 0.006$, $\phi = 0.180$), and TD ($\chi^2 = 7.082$, $P = 0.008$, $\phi = 0.266$) groups (Table 3). Controlling for age, sex, years of education, APOE-ε4 carrier status, depression score, BMI, blood pressure, hypertension treatment, dyslipidemia, and cardiovascular disease, logistic regression mostly confirmed results of χ^2 analyses. The UD group had more p-tau$^+$ individuals than both the EU ($P = 0.006$) and PD ($P = 0.004$) groups, and there was a nonsignificant trend compared with the TD group ($P = 0.056$). There were no group differences in Aβ1-42 profile (P values >0.05). The UD

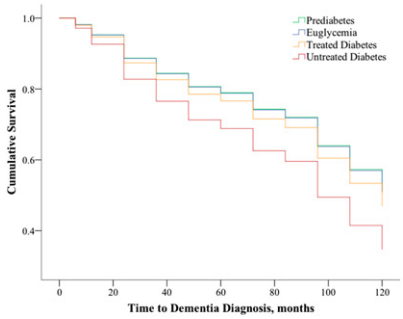

Figure 1—Group differences in pogression to dementia. Cox regression analysis showed the UD group progressed to dementia at a faster rate than the EU group over follow-up (hazard ratio 1.602 [95% CI 1.057–2.429]; P = 0.026). There were no other group differences (P values >0.05).

group had more p-tau$^+$/Aβ1-42$^+$ individuals than the EU (P = 0.014), PD (P = 0.005), and TD (P = 0.005) groups. There were no group by APOE-ε4 carrier status interactions in biomarker profiles (P values >0.05).

Biomarkers and Diabetes Duration

Linear regression analyses showed that diabetes duration was positively associated with both p-tau (P = 0.020; β = 0.118; 95% CI 0.019–0.217) and t-tau (P = 0.014; β = 0.113; 95% CI 0.024–0.202), but not Aβ1-42 (P = 0.377).

Power Analysis

Post hoc power analyses showed both p-tau and t-tau analyses were adequately powered to find group differences (p-tau: noncentrality parameter λ = 13.61, critical F = 2.62, and power = 0.89; t-tau: noncentrality parameter λ = 13.63, critical F = 2.62, and power = 0.89), but the Aβ1-42 analysis was not (noncentrality parameter λ = 1.47; critical F = 2.62; and power = 0.15). Given prior research that diabetes medications may improve β-amyloid clearance, the power to detect a true difference between the UD and TD groups was calculated using the observed Hedge g. Power was observed to be 0.37 to detect a true difference in Aβ1-42 between the UD and TD groups. In order to have a power of 0.80 to detect the difference observed in these data, the sample size would have needed to be substantially greater (UD: n = 129; TD: n = 171).

CONCLUSIONS

To our knowledge, no human in vivo study has explored the relationship between type 2 diabetes treatment and AD pathophysiology. Although type 2 diabetes has previously been linked to tau pathology (24), the current study clarifies the role of treatment status in modifying this association. Our results indicated that older adults with UD exhibited higher CSF p-tau than those with EU, PD, or treated type 2 diabetes. Older adults with UD also showed a more rapid progression to dementia than euglycemic adults. In individuals with TD, diabetes duration was positively associated with p-tau, suggesting that chronic hyperglycemia is associated with more tau dysfunction. Older adults with TD did not differ from either individuals with EU or PD on biomarkers or progression to dementia, suggesting that pharmacotherapy for type 2 diabetes attenuates risk for diabetes-associated dementia. Consistent with our findings, multiple studies have shown that diabetes treatment and well-controlled diabetes reduce the risk for dementia (7,15). Our results bolster the hypothesis that the relationship between type 2 diabetes and tau pathology may be driven by those with UD or poorly managed diabetes. Causal inferences are prohibited by the observational and cross-sectional nature of our biomarker analyses; nevertheless, the findings suggest that treatment status may modify the relationship between type 2 diabetes and both tau-mediated neurodegeneration and dementia.

The relationship between hyperglycemia and p-tau is consistent with findings from animal research. Neuropathological studies in animal models of type 2 diabetes show increased tau phosphorylation and cleavage, neurite degeneration, and neuronal loss (32). Cell culture models suggest that insulin resistance produces p-tau through reduced phosphatidylinositol 3-kinase–Akt activity and downstream activation of GSK3β, providing one possible mechanistic link between insulin resistance and tau pathology. Chronic hyperglycemia is associated with increased advanced glycation end products, which are associated with neurofibrillary tangles (33). Thus, the differences in tau profiles between treated diabetes and UD could be directly related to improved glycemic control. Other neuroprotective effects of the various diabetes medications may have played a role in these observations.

The heterogeneity and sample size of the treated groups precluded examination of individual medications, but the most prescribed diabetes medication in the current study was metformin. Metformin decreases p-tau in animal models (18). The relationship between metformin and risk for dementia is mixed, but several studies show metformin ameliorates risk for dementia (15,16). GLP-1 agonists are also hypothesized to have neuroprotective effects (21), but they were not widely used in the current sample; thus, they cannot account for the positive findings seen. Further research is needed to evaluate the effect of specific medications on tau pathology in humans.

Table 3—CSF biomarker data

	EU (n = 530)	PD (n = 250)	UD (n = 54)	TD (n = 67)	F or χ^2	P value	Partial η^2 or ϕ
p-tau	25.54 (12.97)	25.05 (11.89)	33.26 (19.24)	25.37 (14.23)	4.316	0.005[a]	0.015
t-tau	266.54 (117.24)	264.46 (107.07)	335.26 (156.58)	270.80 (131.90)	4.512	0.004[a]	0.015
Aβ1-42	886.89 (366.82)	904.35 (373.14)	836.50 (346.68)	958.29 (357.30)	0.478	0.698	0.002
p-tau/Aβ1-42	0.04 (0.03)	0.04 (0.03)	0.05 (0.04)	0.03 (0.02)	3.601	0.013[a]	0.015
t-tau/Aβ1-42	0.38 (0.27)	0.36 (0.24)	0.52 (0.38)	0.34 (0.21)	2.568	0.053[b]	0.011
p-tau$^+$ (%)	46.2	43.0	66.7	44.1	10.230	0.017[a]	0.107
Aβ1-42$^+$ (%)	64.3	63.9	67.4	53.4	4.041	0.257	0.074
p-tau$^+$/Aβ1-42$^+$ (%)	40.0	36.5	59.5	32.8	8.922	0.030[a]	0.110

Data are mean (SD) unless otherwise indicated. [a]UD > EU = PD = TD. [b]UD > EU = PD.

Animal and human studies have also linked glucose levels to β-amyloid pathology. Middle-aged adults with type 1 diabetes have greater β-amyloid than control subjects (34), suggesting that insulin may enhance β-amyloid clearance. In a postmortem study of type 2 diabetes, patients who took both insulin and oral hypoglycemic medications had less neuritic plaques in the entorhinal cortex and amygdala compared with monotherapy groups (35). Treatment with metformin in mice is associated with decreased β-amyloid deposition and levels compared with untreated mice (36). Taken together, these studies suggest that several types of diabetes treatments may lower cerebral β-amyloid levels. In the current study, we did not find any significant group differences in β-amyloid; however, post hoc power analyses demonstrated that the β-amyloid analysis was underpowered, making it difficult to draw conclusions. Interestingly, examination of group means revealed that the UD group had the most Aβ1-42, whereas the TD group had the least Aβ1-42. Although these groups did not differ significantly in ANCOVA pairwise comparisons, the treated group showed a small effect for less β-amyloid pathology than the untreated group. p-tau/Aβ1-42 and t-tau/Aβ1-42 were also elevated in individuals with UD, further suggesting that UD may be associated with both increased p-tau and β-amyloid pathology. Similarly, higher tau/β-amyloid ratios are associated with cognitive decline in nondemented adults (37). Future studies with greater sample size may better determine whether there may be a small association between diabetes treatment status and cerebral β-amyloid levels.

Taken together, the tau and β-amyloid findings do not support a relationship between treated type 2 diabetes and AD. Participants with TD did not differ on any CSF biomarkers or ratios from participants with EU. However, older adults with UD showed elevated tau pathology, but did not significantly differ in β-amyloid pathology. In fact, as described above, there was only some evidence of difference in β-amyloid pathology between participants with TD and UD, which may speak to β-amyloid clearance mechanisms associated with type 2 diabetes medications. Thus, we conclude that untreated hyperglycemia appears to be strongly associated with tau pathology, but there is lack of evidence for a relationship between hyperglycemia and β-amyloid, suggesting that hyperglycemia is not associated with typical AD pathophysiological presentation.

Several other cardiovascular risk factors, including hypertension, dyslipidemia, and cardiovascular disease, have been associated with AD risk (38). These factors were included in every analysis supporting that diabetes contributes to differences in p-tau, t-tau, and ratios independent of these risk factors. The UD group did not have greater blood pressure, hypertension treatment, or history of cardiovascular disease compared with other groups and therefore cannot explain the relationship between UD and increased tauopathy. Thus, although cardiovascular risk factors have been shown to increase risk for AD, these factors do not explain the current study findings. Similarly, depression scores were included as a covariate in every analysis and did not affect findings, which may be due to current depression as an exclusion criterion.

It is important to note that the ADNI cohort may not be representative of the aging population with diabetes. The ADNI cohort may be in better overall health, particularly with regard to cardiovascular health, because cerebrovascular disease was part of the exclusion criteria (e.g., Hachinski score cutoff). The prevalence of type 2 diabetes in the current study is 13.5%, whereas it is estimated that 25% of people aged 65 years and older have type 2 diabetes in the U.S. (39). In addition, participants with TD were more likely to be male (63.2% male). Women aged 75 years and older may have greater rates of hypertension, hyperlipidemia, and diabetes compared with men of same age (40). The underrepresentation of women in the sample may mean that differences between groups with diabetes and the euglycemic group are underrepresented. Future studies would benefit from analyzing sex separately if adequately powered.

The most important limitation of the current study is confound by indication. The use of diabetes medication may be a risk indicator for the severity of hyperglycemia and/or longer duration of illness. The generalizability of this study may be compromised due to the nature of the ADNI participant selection and potential recruitment biases specific to each study center. Participants were screened for many vascular issues; the sample likely has less vascular risk factors than the general population. At the same time, this may represent a strength of the study, as we can better isolate how type 2 diabetes and hyperglycemia are related to markers of neurodegenerative disease independent of a more severe vascular risk factor profile. Another limitation is the definition of the different groups based on one fasting blood glucose measure. HbA_{1c} data were not collected in this study and would likely have improved diabetes group classification. Another limitation is the lack of data regarding medication adherence; thus, the current study measured prescription patterns as a proxy for treatment. It is possible that some people in the TD group were not taking their medication as prescribed. If true, our results may be more conservative because if participants were fully compliant, the differences among groups may have been stronger. Lastly, although self-reported diabetes duration and complications data were included, there were no data about hypoglycemic episodes, which could adversely affect cognition.

Despite these limitations, this is, to our knowledge, the first clinical study to investigate differences in type 2 diabetes treatment status on CSF AD biomarkers. Another strength of the current study was the longitudinal design of this study allowed us to examine relationships between treatment and dementia risk.

In summary, the current study demonstrated that UD, but not TD, was associated with elevated p-tau and t-tau and increased p-tau/Aβ1-42 ratio relative to euglycemic individuals. In line with these findings, individuals with UD also showed faster progression to dementia relative to individuals with EU. The findings suggest that hyperglycemia may be linked to tau-mediated processes and that diabetes medication may alter the relationship between tau pathology and hyperglycemia. Further research is needed to elucidate the mechanism with which TD decreases tauopathy associated with hyperglycemia.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Data used in preparation of this article were obtained from the 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.

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