Original Research

Cognitive and Functional Decline in Patients With Mild Alzheimer Dementia With or Without Comorbid Diabetes

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ABSTRACT

Purpose: Although diabetes is recognized as a risk factor for the development of cognitive impairment and for accelerated progression to Alzheimer disease (AD), it is unclear whether patients with diabetes who have already progressed to AD have a different rate of cognitive and functional decline compared with that in those without diabetes. This post hoc exploratory analysis compared cognitive and functional decline over an 18-month period in patients with mild AD dementia with and without comorbid diabetes. Decline in quality of life was assessed as a secondary objective.

Methods: In a post hoc exploratory analysis, we analyzed data from the placebo groups of three 18-month, randomized, placebo-controlled trials of solanezumab and semagacestat in patients with AD. Data from patients with mild AD dementia (Mini-Mental State Examination [MMSE] score, 20–26) and comorbid diabetes at baseline were compared with data from patients with mild AD dementia without diabetes at baseline. Cognition was assessed using the 14-item AD Assessment Scale–Cognitive Subscale ($ADAS\text{-}Cog_{14}$) and the MMSE. Functioning was assessed with the AD Cooperative Study–Activities of Daily Living Inventory (instrumental subset) (ADCS-iADL). Quality of life was assessed using the European Quality of Life–5 Dimensions scale, proxy version (proxy utility score and visual analog scale score), and the Quality of Life in AD scale, self-report and proxy (caregiver) versions. Group comparisons of changes from baseline to 18 months in cognitive, functional, and quality-of-life measures employed a repeated-measures model adjusted for propensity score, study, baseline cognition score (functional or quality of life), age, sex, level of education, genotype of the apolipoprotein E gene, and concurrent use of an acetylcholinesterase inhibitor or memantine.

Findings: At baseline, patients with mild AD dementia with and without diabetes did not significantly differ on the cognitive measures, but those without diabetes were functioning at a significantly higher level. At 18 months, compared with patients without diabetes, those with diabetes showed a numerically but statistically nonsignificantly lesser cognitive decline (least squares mean between-group differences: $ADAS\text{-}Cog_{14}$ score, 1.61 [$P = 0.21$]; MMSE score, –0.40 [$P = 0.49$]) and a statistically significantly lesser functional decline (least squares mean between-group difference in ADCS-iADL score, –3.07; $P = 0.01$). The 2 groups did not differ on declines in the quality-of-life measures.

Implications: The present findings suggest that diabetes may influence the rate of functional decline among patients with mild AD dementia. These results require replication in studies that address the limitations of the present post hoc exploratory analysis and that explore the potential causes of the observed differences. (*Clin Ther.* 2015;37:1195–1205) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

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Key words: Alzheimer disease, clinical trial, cognition, diabetes, functioning, quality of life.

INTRODUCTION

Alzheimer disease (AD) and type 2 diabetes are chronic diseases that may share common pathologic features (eg, amyloid formation),[1–3] in addition to being linked to the aging process.[4] Diabetes is associated with the development of cognitive impairment[5–8] and with accelerated progression to dementia due to AD.[9] Some evidence suggests that AD is associated with a brain-specific type of insulin resistance and that insulin signaling may be attenuated in parts of the brain in patients with AD.[10,11] Insulin receptors are found in the memory-foundation regions of the brain,[12] and it is speculated that stimulation of insulin-receptor signaling in these brain regions with some of the glucose-lowering drugs, such as insulin, thiazolidinediones, and glucagon-like polypeptide-1 receptor agonists, may benefit patients with AD. Clinical trials of glucose-lowering drugs as alternative treatments in patients with AD have been undertaken.[13–16]

The association between mild cognitive impairment and diabetes is known.[17,18] Mild cognitive impairment represents a transitional phase between normal cognitive function and dementia, although not all people with mild cognitive impairment progress to develop dementia.[19] It is unclear whether diabetic patients who have already progressed to dementia due to AD experience a different rate of further cognitive and functional decline over time compared with that in patients with AD without diabetes. We hypothesized that the presence of comorbid diabetes is associated with a faster rate of decline in patients with AD. Therefore, we aimed to assess whether patients with mild AD dementia and comorbid diabetes show a greater magnitude of cognitive and functional decline compared with those without comorbid diabetes. The focus on patients with mild AD dementia, rather than moderate or severe AD dementia, was driven by the growing recognition that patients with mild AD dementia are more likely to benefit from disease-modifying interventions, reflecting a greater potential for change in the progression of the disease.[20,21]

The primary objective of this post hoc exploratory analysis was to compare cognitive and functional decline over 18 months between patients with mild AD dementia with and without a comorbid diabetes diagnosis. As a secondary objective, this analysis compared the decline in quality of life in patients with mild AD dementia with and without comorbid diabetes. In addition, as an exploratory objective, we repeated the analyses on data from patients with moderate AD dementia.

PATIENTS AND METHODS

Analysis Population

This post hoc exploratory analysis used data from the placebo groups of three 18-month, randomized, placebo-controlled trials of solanezumab and semagacestat in patients with AD.[22,23] The analysis population was created from the intent-to-treat populations of the placebo groups. Specifically, patients with mild AD dementia (Mini-Mental State Examination [MMSE] score, 20–26) and comorbid diabetes at baseline were compared with patients with mild AD without diabetes at baseline. The analysis was repeated on data from patients with moderate AD dementia (MMSE score, 16–19), comparing those with comorbid diabetes at baseline to those with without diabetes at baseline.

Patient Consent

The parent studies[22,23] received ethical approval from the governing institutional review boards, and patients and caregivers provided written informed consent in accordance with the Declaration of Helsinki.

Assessment of Diabetes

The presence of diabetes as a condition comorbid with AD was assessed at baseline as a part of patient-reported medical comorbidities. For the purposes of the present analyses, *comorbid diabetes* was defined as the presence of at least 1 of the following criteria: baseline random blood glucose concentration $\geq$200 mg/dL (11.1 mmol/L), patient-reported preexisting diabetes at or before baseline, and/or reported use of any glucose-lowering medication at or before baseline (a sulfonylurea [tolbutamide, glibenclamide, gliclazide, glimepiride, glipizide, glibenclamide/metformin], a biguanide [buformin, metformin], a thiazolidinedione [pioglitazone, rosiglitazone, pioglitazone/metformin, rosiglitazone/metformin], an α-glucosidase inhibitor [acarbose, miglitol, voglibose], a dipeptidyl peptidase 4 inhibitor [saxagliptin, sitagliptin, vildagliptin, sitagliptin/metformin], a meglitinide [nateglinide, repaglinide], glucagon-like

peptide-1 receptor agonists [exenatide], insulins [insulin human, insulins and analogues, insulin aspart, insulin bovine, insulin lispro, insulin porcine, insulin lispro human analogue + protamine, recombinant human insulins, insulin aspart + protamine, insulin detemir, insulin glargine], and/or epalrestat). Patients who did not meet any of the preceding criteria were categorized as being without comorbid diabetes. No information was available on the type of diabetes, duration of diabetes, or its severity.

Measures of Cognition, Functioning, and Quality of Life

Cognitive decline was measured by the 14-item AD Assessment Scale–Cognitive subscale [ADAS-Cog_{14}] and the MMSE. The ADAS-Cog_{14} was designed to assess cognitive impairment in persons with AD; total scores range from 0 to 90, with higher scores indicating greater disease severity.[24] The MMSE is a brief, 2-part measure used for assessing cognitive function.[25] The range of the total MMSE score is 0 to 30, with lower scores indicating greater severity of disease.

Functional decline was measured with the AD Cooperative Study–Activities of Daily Living Inventory (instrumental subset) [ADCS-iADL]).[26] The ADCS-iADL is an inventory developed as a rater-administered questionnaire that is answered by the patient's caregiver. The caregiver is asked whether the patient has attempted activities of daily living within the preceding 4 weeks. If the patient has done so, the caregiver is asked to rate the patient's performance level based on a set of performance descriptions. Scores range from 0 to 56, with higher scores indicating better functioning in performing activities of daily living.

Quality of life was assessed using 4 health-related quality-of-life measures: the European Quality of Life–5 Dimensions (EQ-5D)[27]; the Health-Related Quality of Life Scale, proxy version, utility score; the EQ-5D visual analog scale score; and the Quality of Life in AD scale, self-report and caregiver versions[28,29] (QoL-AD-Self and QoL-AD-Caregiver, respectively).

Baseline Characteristics

The baseline characteristics of the analysis population were summarized by mild AD with and without comorbid diabetes at baseline and overall. Summaries included descriptive statistics for continuous and categorical measures. The Fisher exact test or Pearson χ^2 test was used for comparing the categorical data between the diabetic and nondiabetic groups. For continuous data, ANOVA was used.

Statistical Analysis

The 3 studies from which the data were extracted were not designed for investigating the relationships between diabetes and AD progression. A propensity score was applied to each patient to adjust for potential imbalance in core baseline characteristics (ie, age, body mass index [BMI], sex, and antihypertensive drug use) between the diabetic and nondiabetic groups. The propensity score in each patient was calculated using a logistic regression model, with diabetes status as the dependent variable and with baseline age, BMI, sex, and antihypertensive drug use at baseline as independent variables.

Declines in cognition, functioning, and quality-of-life measures over the 18-month study were assessed as absolute magnitudes of change from baseline to 18 months (week 76[22] or 80[23]).

Cognitive decline over 18 months was assessed using the ADAS-Cog_{14} and MMSE, with between-group comparisons made using a mixed-effects, repeated-measures (MMRM) model adjusted for propensity score, study, baseline score, age, sex, level of education (stratified as <8, 8–12, and >12 years), genotype of the apolipoprotein E gene (*APOE*), and concurrent use of an acetylcholinesterase inhibitor (AChEI) or memantine. Two sensitivity analyses were conducted to assess the robustness of the findings (details in the Sensitivity Analyses section).

Functional decline was assessed using the ADCS-iADL, which employed an MMRM model adjusted for propensity score, study, baseline score, age, sex, level of education, *APOE* genotype, and concurrent AChEI or memantine use. A similar analysis was conducted on data from each of the 4 quality-of-life measures.

These analyses were repeated on data from patients with moderate AD. All data analyses were carried out using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

Sensitivity Analyses

Two sensitivity analyses were employed for each instrument—ADAS-Cog_{14}, MMSE, and ADCS-iADL—by changing the generation of propensity score. The first new propensity score was created based on sex, BMI, and age only, excluding antihypertensive drug use from the original model. Antihypertensive drug use was then added as a covariate in the primary

MMRM model together with the new propensity score, study, baseline score, visit, baseline age, sex, diabetes status at baseline, level of education (stratified as <8, 8–12, and >12 years), *APOE* genotype, and concurrent AChEI or memantine use. Similarly, the second new propensity score was created based on sex and age only, excluding antihypertensive drug use and BMI from the original model. BMI was added to the primary MMRM model as a covariate along with the new propensity score, study, baseline score, visit, baseline age, sex, diabetes status at baseline, level of education (stratified as <8, 8–12, and >12 years), *APOE* genotype, and concurrent AChEI or memantine use. The statistical adjustment included BMI because a previous study found that the risk for cognitive decline was decreased among overweight and obese patients.[30]

RESULTS

Baseline Characteristics of Patients with Mild AD

A total of 972 patients with mild AD (113 diabetic and 859 nondiabetic) were included in the analysis and were followed up for 18 months (Table). The groups with and without diabetes did not significantly differ in terms of years of education, substance (alcohol, caffeine, or tobacco) use, *APOE ε4* carrier status, work status, time since onset of AD symptoms, or time since AD diagnosis. Patients with diabetes were statistically significantly more likely to be male, have a greater BMI, have a higher baseline Neuropsychiatric Inventory score, and be using a blood glucose–lowering and/or antihypertensive drug. The diabetic patients had a statistically significant lower (poorer) mean baseline functional (ADCS-iADL) score compared with the nondiabetic patients. The patients without diabetes felt better at baseline than did the patients with diabetes (QoL-AD-Self).

Changes in Cognition

These patients with mild AD with or without diabetes had worsening on both cognitive measures—ADAS-Cog_{14} and MMSE—at the end of the follow-up period (Figures 1 and 2). The between-group difference in score on either measure was not statistically significant (least squares mean [LSM] differences at 18 months: ADAS-Cog_{14}, –1.61 [95% CI, –4.16 to 0.93; $P = 0.21$]; MMSE, –0.40 [95% CI, –1.52 to 0.73; $P = 0.49$]). Compared with the group without diabetes, the diabetic group showed numerically, but not statistically significantly, lesser declines (by 26% on the ADAS-Cog_{14} and by 20% on the MMSE). The 2 sensitivity analyses yielded similar results.

Changes in Functional Ability

Although all of the patients with mild AD had functional decline over the follow-up period (Figure 3), the patients with diabetes demonstrated a significantly lesser magnitude of decline at 18 months (LSM difference on ADCS-iADL, –3.07; 95% CI, 0.62–5.53; $P = 0.01$). The 3.07-point difference translates into 46% lesser decline in the diabetes group. During the 18-month follow-up, the nondiabetic group had a decline of 5.87, from 43.00 to 37.13, whereas the diabetic group changed very little on the ADCS-iADL measure (decline of 0.54 points, from 40.77 to 40.23). The 2 sensitivity analyses provided essentially the same, significant, results.

Changes in Quality of Life

Scores on all 4 quality-of-life measures suggested declines in both patient groups at 18 months, except in patients with diabetes on the EQ-5D utility score, which remained similar. The magnitudes of change from baseline to 18 months were not significantly different between the diabetic and nondiabetic groups on any of the 4 quality-of-life measures. On the ED-5Q visual analog scale measure, the LSM difference at 18 months was 1.86 (95% CI, –2.94 to 6.66; $P = 0.45$). On the EQ-5D utility score, the LSM difference was –0.02 (95% CI, –0.08 to 0.03; $P = 0.41$). The LSM differences on the QoL-AD-Caregiver and QoL-AD-Self scales in patients with mild AD with and without comorbid diabetes were –1.00 (95% CI, –2.50 to 0.51; $P = 0.45$) and –0.11 (95% CI, –1.54 to 1.32; $P = 0.88$), respectively.

Patients with Moderate AD

When the analyses were repeated in patients with moderate AD dementia with (n = 59) and without (n = 494) diabetes, the 2 groups did not significantly differ on baseline characteristics, except for a longer time since AD diagnosis before baseline in the diabetic patients (3.2 years vs 2.6 years in the nondiabetic patients; $P = 0.05$) and having 1 or more primary relatives with AD (19% of the diabetic patients had a primary relative with AD, whereas 36% of the nondiabetic patients had a primary relative with AD; $P = 0.01$) (data not shown).

When compared on magnitude of decline in cognitive, functional, and quality-of-life measures over the 18-month study, the patients with moderate AD

Table. Baseline demographic and clinical characteristics of the diabetic and nondiabetic patients with mild Alzheimer disease (intent to treat).

Characteristic	Diabetic (n = 113)	Nondiabetic (n = 859)	*P*
Sociodemographic			
Age, mean (SD), y	74 (8)	74 (8)	0.491
Male sex, no. (%)	64 (56.6)	393 (45.8)	0.029
Race, no. (%)			0.600
White	91 (80.5)	728 (84.7)	
Asian	16 (14.2)	105 (12.2)	
Hispanic	4 (3.5)	12 (1.4)	
Other	2 (1.8)	14 (1.6)	
Education, years, mean (SD)	12.3 (3.9)	12.6 (3.9)	0.410
Work status, no. (%)			0.271
Retired	92 (81.4)	732 (85.2)	
Unable to work	9 (8.0)	48 (5.6)	
Full-time	6 (5.3)	21 (2.4)	
Part-time	5 (4.4)	37 (4.3)	
Volunteer work	1 (0.9)	21 (2.4)	
Does not live alone or own home, no. (%)	100/107 (93.5)	724/818 (88.5)	0.123
Clinical			
BMI, mean (SD), kg/m^2	27.4 (4.9)	25.2 (4.2)	<0.001
Risk factors, no. (%)			
Substance use			
Caffeine	47/70 (67.1)	405/593 (68.3)	0.845
Alcohol	35 (31.0)	347 (40.4)	0.054
Tobacco	6 (5.3)	63 (7.3)	0.431
APOE			
ε4 carrier	53/101 (52.5)	466/782 (59.6)	0.172
Genotype			
ε2/ε4	2/101 (2.0)	25/782 (3.2)	
ε3/ε4	41/101 (40.6)	328/782 (41.9)	
ε4/ε4	10/101 (9.9)	113/782 (14.5)	
Primary relative(s) with AD	43/99 (43.4)	309/787 (39.3)	0.424
AD history			
Time since onset of AD symptoms, mean (SD), y	4.0 (2.6)	4.3 (2.6)	0.330
Time since AD diagnosis, mean (SD), y	1.8 (1.8)	2.0 (1.8)	0.417
AD scale scores			
GDS			
Mean (SD) score	1.8 (1.5)	1.9 (1.5)	0.600
Status, no. (%)			1.000
6 (at least mild depression)	2 (1.8)	16 (1.9)	
≤ 5 (normal)	111 (98.2)	843 (98.1)	
MMSE score, mean (SD)			
Visit 1, screening	22.9 (2.0)	22.9 (2.0)	0.878
Visit 2, baseline	22.6 (2.8)	22.6 (2.8)	0.978

(continued)

Table. (continued).

Characteristic	Diabetic (n = 113)	Nondiabetic (n = 859)	*P*
Modified HIS, mean (SD)	0.9 (0.8)	0.7 (0.8)	0.119
ADAS-Cog$_{14}$ score, mean (SD)	29.2 (9.7)	29.5 (8.6)	0.667
ADCS-iADL score, mean (SD)	40.8 (11.1)	43.0 (9.6)	0.024
EQ-5D score, mean (SD)			
VAS	70.3 (21.0)	71.7 (21.7)	0.516
Utility	0.82 (0.14)	0.85 (0.13)	0.068
QoL-AD, mean (SD)			
Self	36.4 (5.3)	38.1 (6.1)	0.037
Caregiver	34.0 (5.9)	35.3 (6.1)	0.114
NPI total score, mean (SD)	11.9 (13.0)	9.0 (11.1)	0.012
Current treatment, no. (%)[*]			
AChEI/memantine	93 (82.3)	758 (88.2)	0.072
Antidiabetic	82/113 (72.6)	–	–
Antihypertensive	73 (64.6)	371 (43.2)	<0.001
Insulin[†]	17 (15.0)	–	–

AChEI = acetylcholinesterase inhibitor; AD = Alzheimer disease; ADAS-Cog$_{14}$ = 14-item Alzheimer's Disease Assessment Scale–Cognitive subscale (scale: 0– 90, with higher scores indicating greater disease severity); ADCS-iADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (instrumental subset) (scale: 0–56, with higher scores indicating better functioning in performing activities of daily living); *APOE* = apolipoprotein E gene; BMI = body mass index; DDP-4 = dipeptidyl peptidase 4; GDS = Geriatric Depression Scale (scale: 0-5, normal in elderly with mild-moderate dementia); patients with GDS > 6 at screening were excluded from trials; EQ-5D = European Quality of Life–5 Dimensions; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HIS = Hachinski Ischemic Scale (scale: <4, primary dementia [eg, Alzheimer disease]; >4 suggest that a patient's dementia is likely to be vascular in etiology; these patients were excluded from the trials; 4–7, indeterminate; >7, vascular dementia); MMSE = Mini–Mental State Examination (scale: 0–30, with lower scores indicating greater severity of disease); NPI = Neuropsychiatric Inventory (total of frequency of symptoms [4-point scale] + severity of symptoms [3-point scale] + distress caused by symptoms [5-point scale]); QoL-AD = Quality of Life in Alzheimer's Disease (13 items rated on a 4- point scale, with 1 being poor and 4 being excellent; scale: 13–52, with higher scores indicated better quality of life); VAS = visual analog scale.

[*]At baseline, patients were receiving a sulfonylurea (including tolbutamide, glibenclamide, gliclazide, glimepiride, and glipizide), a biguanide (including buformin and metformin), a thiazolidinedione (including pioglitazone and rosiglitazone), an α-glucosidase inhibitor (including acarbose, miglitol, and voglibose), a dipeptidyl peptidase 4 inhibitor (including saxagliptin, sitagliptin, vildagliptin, and sitagliptin/metformin), a meglitinide (including nateglinide and repaglinide), glibenclamide/metformin, glibenclamide/metformin, pioglitazone/metformin, rosiglitazone/metformin, or epalrestat.

[†]May have included insulin human, insulin analogues, insulin aspart, insulin bovine, insulin lispro, insulin porcine, insulin lispro human analogue + protamine, recombinant human insulin, insulin aspart + protamine, insulin detemir, or insulin glargine.

dementia with and without diabetes did not significantly differ on any of the measures.

DISCUSSION

Contrary to our hypothesis, the findings from the present post hoc exploratory analysis suggest that patients with mild AD dementia and comorbid diabetes did not have greater declines in cognition, functional ability, or quality of life compared with those in patients without diabetes. Unexpectedly, the diabetic patients were found to have a statistically significantly lesser functional decline from baseline to end point at 18 months compared with that in those without diabetes, although the patients with AD and diabetes were functioning at a lower level at baseline. The 2 sensitivity analyses suggested robustness of these findings, providing essentially the same results with and without adjustments for potential confounders such as

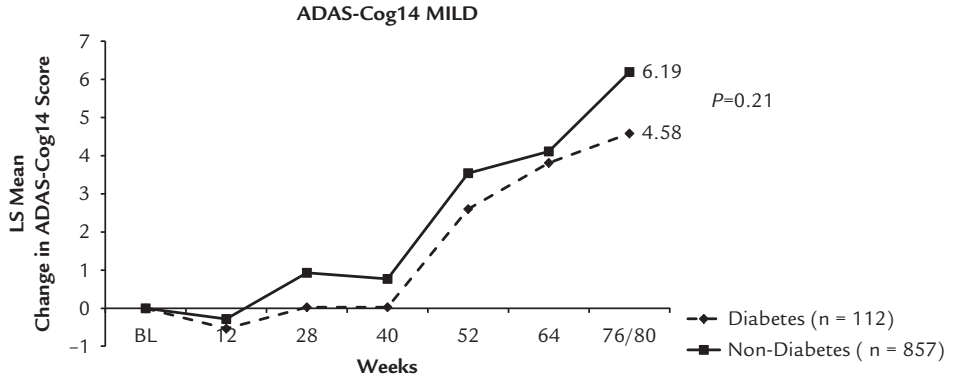

Figure 1. Cognitive functioning, as measured using the 14-item Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog$_{14}$), in patients with mild Alzheimer disease with and without comorbid diabetes. Scale: 0 to 90, with higher scores indicating greater disease severity. Analysis used a propensity score generated by sex, age, body mass index, and antihypertensive treatment status at baseline as covariates in a mixed-effects, repeated-measures model. The least squares mean difference at study end was 1.61 (95% CI, −4.16 to 0.93; $P = 0.21$).

BMI, sex, and antihypertensive drug use. In patients with a more severe form of AD—those diagnosed with moderate AD—the groups with and without comorbid diabetes did not significantly differ on decline in any of the cognitive, functional, or quality-of-life measures.

Although a literature search revealed no published studies comparing cognitive decline among patients with mild AD dementia with diabetes versus those without diabetes, 3 studies in heterogeneous groups of community-dwelling patients with AD have reported diabetes to be associated with a lower magnitude of cognitive decline.[31–33] The first study, in 135 patients with mild to moderate probable or possible AD, reported that diabetes was associated with a slower rate of cognitive decline, as measured with the MMSE and the clinical dementia rating Sum of Boxes, over a

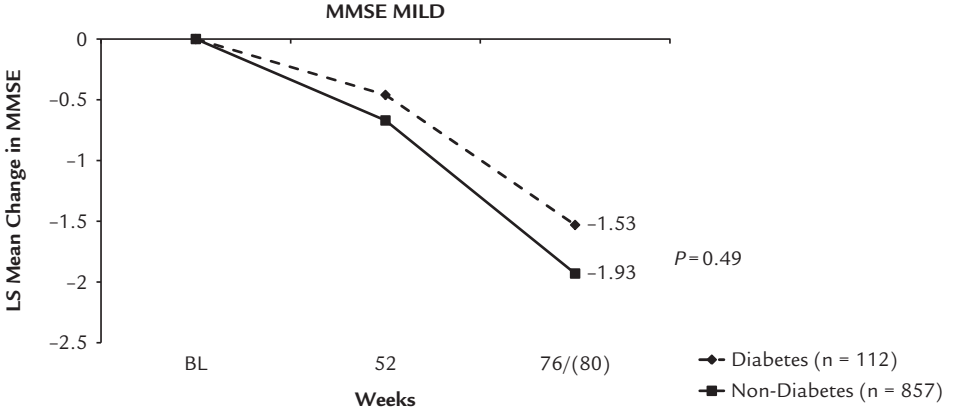

Figure 2. Cognitive functioning, as measured using the Mini–Mental State Examination (MMSE), in patients with mild Alzheimer disease with and without comorbid diabetes. Scale: 0 to 30, with lower scores indicating greater severity of disease. Analysis used a propensity score generated by sex, age, body mass index, and antihypertensive treatment status at baseline as covariates in a mixed-effects, repeated-measures model. The least squares mean difference at study end was −0.40 (95% CI, −1.52 to 0.73; $P = 0.49$).

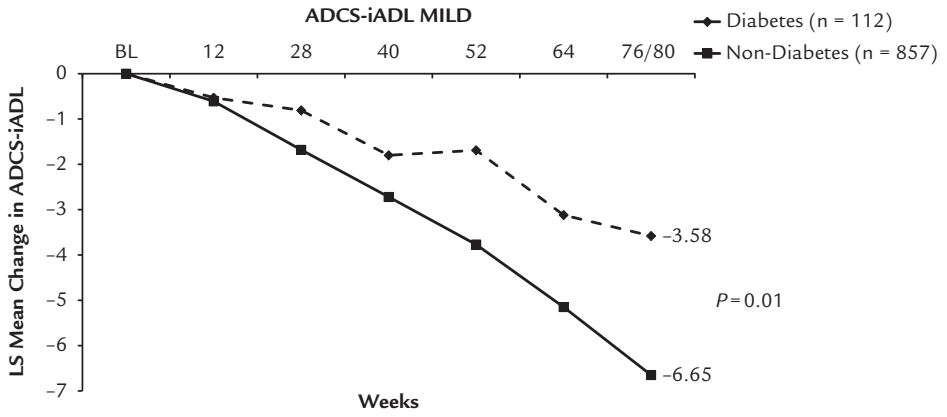

Figure 3. Functional decline, as measured using the Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (instrumental subset) (ADCS-iADL), in patients with mild Alzheimer disease with and without comorbid diabetes. Scale: 0 to 56, with higher scores indicating better functioning in performing activities of daily living. Analysis used a propensity score generated by sex, age, body mass index, and antihypertensive treatment status at baseline as covariates in a mixed-effects, repeated-measures model. The least squares mean difference at study end was −3.07 (95% CI, 0.62–5.53; $P = 0.01$).

mean duration of 3 years.[31] The second study, in 154 patients with mild to moderate AD who were followed up for a mean duration of 23 months, reported that patients with diabetes had a 65% reduced risk for fast cognitive decline compared with patients without diabetes.[32] *Fast decline* was defined as a worsening on the MMSE of ≥ 5 points. The third study followed up 608 patients with mild to moderate AD for a mean duration of 26 months and reported that patients with diabetes had a significantly lesser cognitive decline compared with those without diabetes.[33] The causes of the more favorable course of the disease in the patients with diabetes was not clear; the study authors hypothesized that there may have been differences in underlying neuropathology between the 2 groups (eg, the group with diabetes may have had vascular pathology that contributed to the initial diagnosis and severity of dementia, but a lower burden of AD pathology, that led to the slower rate of decline compared with that in those without diabetes).[33] There also may have been possible protective effects of the antihypertensive and/or antidiabetic drugs taken by those with diabetes.[31–33] In contrast to the patients in those population-based studies, the patients in our analysis were participants in 1 of 3 randomized, placebo-controlled studies of solanezumab or semagacestat. The use of rigorous inclusion and exclusion criteria in these randomized clinical trials likely resulted in differences between our group and those treated in usual-care settings.

The present analysis did not find that patients with and without diabetes differed significantly in cognitive decline, but the diabetes group had numerically lesser magnitudes of decline on both the ADAS-Cog_{14} and the MMSE. The observed numeric between-group differences, which translate into a 26% lesser decline on the ADAS-Cog_{14} and a 20% lesser decline on the MMSE, may be clinically meaningful. In contrast, a 46% lesser functional decline was seen in the patients with diabetes compared with that in the patients without diabetes, as measured by the ADCS-iADL. Our finding of a significant between-group difference in functional decline, with a numeric but nonsignificant between-group difference in cognitive decline, may appear unusual considering the robust link between cognition and functioning in AD, in which the functional deficit is thought to be largely, if not entirely, due to the cognitive deficit.[34,35] However, the presence of comorbid conditions may contribute to functional disability apart from impairments in cognition; patients with diabetes are more likely to have impairments of balance, vision, and strength, all of which can interfere with daily functioning independent of cognition. It is also possible that the observed between-group differences in functional

decline were simply due to a regression to the mean as a result of differences in baseline functional level, with the patients without diabetes functioning at a significantly higher level than those with diabetes.[36]

Most of the diabetic patients in the present analysis (72.6% [82/113]) were receiving treatment with a glucose-lowering medication at baseline; 19.5% of those (16/82) were being treated with insulin. Findings from recent clinical trials suggest that glucose-lowering medications may attenuate cognitive impairment in patients with mild AD.[37] Intranasal insulin use has been reported to delay cognitive decline in murine models,[38] and it has been suggested to preserve cognitive functioning in a small number of adults with mild AD.[13] A larger-scale study of intranasal insulin in mild cognitive impairment and mild AD is underway.[37] Glucagon-like peptide-1 analogues are being tested in patients with AD after a reversal of memory impairment and reduced plaque loads were reported in murine models.[14,39] Early studies suggested that rosiglitazone, a thiazolidinedione (peroxisome proliferator-activated receptor γ agonist), might slow cognitive deterioration in APOE ε4 noncarriers with mild AD; however, a well powered phase 3 study did not show evidence of benefit.[16] Other thiazolidinediones such as pioglitazone have had promising safety profiles in pilot studies, and further trials are being planned.[15]

Study Limitations

This post hoc exploratory analysis used data from patients enrolled in the placebo arms of 3 different studies of 2 investigational agents for mild to moderate AD; none of these studies were designed to address the questions being investigated in the present analysis. Information on patients' diabetes was somewhat limited. No information was collected to help to differentiate between types 1 and 2 diabetes. These two diseases may have different effects on cognitive decline; however, considering the age distributions of the study participants and the substantially greater prevalence of type 2 diabetes versus type 1 in the general population, it is likely that the majority of patients had type 2 diabetes.[40] Information on the duration of diabetes, duration of diabetes medication intake, and hemoglobin A_{1c} measures of diabetes control was not available. These variables are highly relevant to the present analysis, as a previous study in older adults with type 2 diabetes found that the only risk factors associated with cognitiveimpairment were the duration of diabetes and hemoglobin A_{1c} level.[41] Furthermore, an elevated hemoglobin A_{1c} concentration may be a risk factor for dementia and cognitive impairment even in patients who have not yet been diagnosed with diabetes ("prediabetes").[42] In addition, although recent findings have suggested that specific antidiabetic medications may help to attenuate cognitive decline,[15,43] the small sample size of the diabetic group in the present analysis did not allow for a comparison of cognitive decline between the diabetic patients treated with specific oral antidiabetic medications and insulin. Another study limitation was the lack of information about patients' β-amyloid status, which raises the possibility that patients with AD and diabetes might have included those with mixed or vascular types of dementia. Last, the present study included participants from 3 randomized, controlled studies. This fact raises the potential for selection bias of the diabetic patients because the studies may have enrolled patients with well-controlled diabetes, and therefore the studied population may not represent the typical trajectory of decline in patients with comorbid AD and diabetes treated in usual-care settings.

The main strengths of the current analysis included its large sample size of patients with AD with and without comorbid diabetes, the frequent assessments over the 18-month follow-up period, and the use of comprehensive and validated assessment tools.

The present findings will require both replication and additional investigation in patients treated in community care to better address the potential limitations of the present analysis and to better understand the potential determinants of the observed differences.

CONCLUSIONS

The findings from this post hoc exploratory analysis suggests that patients with mild AD dementia with diabetes, although functioning at a lower level at baseline, manifest significantly less functional decline over an 18-month period compared with those without diabetes, whereas cognitive decline and decline in quality of life were not found to significantly differ between the 2 groups. The present findings will require both replication and additional investigation in patients treated in community care to better address the potential limitations of the current analysis.

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CONFLICTS OF INTEREST

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REFERENCES

1. Janson J, Laedtke T, Parisi JE, et al. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes*. 2004;53:474–481, http://dx.doi.org/10.2337/diabetes.53.2.474.
2. Knowles TP, Vendruscolo M, Dobson CM. The amyloid state and its association with protein misfolding diseases. *Nat Rev Mol Cell Biol*. 2014;15:384–396, http://dx.doi.org/10.1038/nrm3810.
3. Ryan JP, Fine DF, Rosano C. Type 2 diabetes and cognitive impairment: contributions from neuroimaging. *J Geriatr Psychiatry Neurol*. 2014;27:47–55, http://dx.doi.org/10.1177/0891988713516543.
4. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol*. 2008;7:184–190, http://dx.doi.org/10.1016/S1474-4422(08)70021-8.
5. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. *Diabetologia*. 2005;48:2460–2469, http://dx.doi.org/10.1007/s00125-005-0023-4.
6. Gregg EW, Yaffe K, Cauley JA, et al, Osteoporotic Fractures Research Group. Is diabetes associated with cognitive impairment and cognitive decline among older women? *Arch Intern Med*. 2000;160:174–180, http://dx.doi.org/10.1001/archinte.160.2.174.
7. Ott A, Stolk RP, van Harskamp F, et al. Diabetes mellitus and the risk of dementia: the Rotterdam study. *Neurology*. 1999;53:1937–1942, http://dx.doi.org/10.1212/WNL53.9.1937.
8. Roberts RO, Knopman DS, Geda YE, et al. Association of diabetes with amnestic and nonamnestic mild cognitive impairment. *Alzheimers Dement*. 2014;10:18–26 http://dx.doi.org/10.1016/j.jalz.2013.01.001.
9. Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 2006;5:64–74, http://dx.doi.org/10.1016/S1474-4422(05)70284-2.
10. Akter K, Lanza EA, Martin SA, et al. Diabetes mellitus and Alzheimer's disease: shared pathology and treatment? *Br J Clin Pharmacol*. 2011;71:365–376, http://dx.doi.org/10.1111/j.1365-2125.2010.03830.x.
11. Moloney AM, Griffin RJ, Timmons S, et al. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. *Neurobiol Aging*. 2010;31:224–243, http://dx.doi.org/10.1016/j.neurobiolaging.2008.04.002.
12. McNay EC, Recknagel AK. Brain insulin signaling: a key component of cognitive processes and a potential basis for cognitive impairment in type 2 diabetes. *Neurobiol Learn Mem*. 2011;96:432–442, http://dx.doi.org/10.1016/j.nlm.2011.08.005.
13. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. *Arch Neurol*. 2012;69:29–38, http://dx.doi.org/10.1001/archneurol.2011.233.
14. Egefjord L, Gejl M, Møller A, et al. Effects of liraglutide on neurodegeneration, blood flow and cognition in Alzheimer's disease—protocol for a controlled, randomized double-blinded trial. *Dan Med J*. 2012;59:A4519.
15. Geldmacher DS, Fritsch T, McClendon MJ, et al. A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease. *Arch Neurol*. 2011;68:45–50, http://dx.doi.org/10.1001/archneurol.2010.229.
16. Gold M, Alderton C, Zvartau-Hind M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. *Dement Geriatr Cogn Disord*. 2010;30:131–146, http://dx.doi.org/10.1159/000318845.
17. Artero S, Ancelin ML, Portet F, et al. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurg Psychiatry*. 2008;79:979–984, http://dx.doi.org/10.1136/jnnp.2007.136903.
18. Xu W, Caracciolo B, Wang HX, et al. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. *Diabetes*. 2010;59:2928–2935, http://dx.doi.org/10.2337/db10-0539.
19. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256:240–246, http://dx.doi.org/10.1111/j.1365-2796.2004.01380.x.
20. Carlson C, Sundell K, Estergard W, et al. Efficacy of solanezumab in patients with mild or moderate Alzheimer's disease: pooled analyses findings from two phase III studies [abstract]. *Alzheimers Diment*. 2013;9(4 Suppl):139, http://dx.doi.org/10.1016/j.jalz.2013.04.082.
21. Cummings JL, Doody R, Clark C. Disease-modifying therapies for Alzheimer disease: challenges to early intervention. *Neurology*. 2007;69:1622–1634, http://dx.doi.org/10.1212/01.wnl.0000295996.54210.69.
22. Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369:341–350, http://dx.doi.org/10.1056/NEJMoa1210951.
23. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370:311–321, http://dx.doi.org/10.1056/NEJMoa1312889.

24. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(Suppl 2):S13–S21, http://dx.doi.org/10.1097/00002093-199700112-00003.
25. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198, http://dx.doi.org/10.1016/0022-3956(75)90026-6.
26. Galasko D, Kershaw PR, Schneider L, et al. Galantamine maintains ability to perform activities of daily living in patients with Alzheimer's disease. *J Am Geriatr Soc*. 2004;52:1070–1076, http://dx.doi.org/10.1111/j.1532-5415.2004.52303.x.
27. Kind P. The EuroQoL Instrument: an index of health-related quality of life. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1996:191–201.
28. Logsdon RG, Gibbons LE, McCurry SM, et al. Assessing quality of life in older adults with cognitive impairment. *Psychosom Med*. 2002;64:510–519, http://dx.doi.org/10.1097/00006842-200205000-00016.
29. Thorgrimsen L, Selwood A, Spector A, et al. Whose quality of life is it anyway? The validity and reliability of the Quality of Life–Alzheimer's Disease (QoL-AD) scale. *Alzheimer Dis Assoc Disord*. 2003;17:201–208, http://dx.doi.org/10.1097/00002093-200310000-00002.
30. Doruk H, Naharci MI, Bozoglu E, et al. The relationship between body mass index and incidental mild cognitive impairment, Alzheimer's disease and vascular dementia in elderly. *J Nutr Health Aging*. 2010;14:834–838, http://dx.doi.org/10.1007/s12603-010-0113-y.
31. Mielke MM, Rosenberg PB, Tschanz J, et al. Vascular factors predict rate of progression in Alzheimer disease. *Neurology*. 2007;69:1850–1858, http://dx.doi.org/10.1212/01.wnl.0000279520.59792.fe.
32. Musicco M, Palmer K, Salamone G, et al. Predictors of progression of cognitive decline in Alzheimer's disease: the role of vascular and sociodemographic factors. *J Neurol*. 2009;256:1288–1295, http://dx.doi.org/10.1007/s00415-009-5116-4.
33. Sanz C, Andrieu S, Sinclair A, et al. Diabetes is associated with a slower rate of cognitive decline in Alzheimer disease. *Neurology*. 2009;73:1359–1366, http://dx.doi.org/10.1212/WNL.0b013e3181bd80e9.
34. Liu-Seifert H, Siemers E, Sundell K, et al. Cognitive and functional decline and their relationship in patients with mild Alzheimer's dementia. *J Alzheimers Dis*. 2014, http://dx.doi.org/10.3233/JAD-140792. [Epub ahead of print].
35. Zahodne LB, Manly JJ, Mackay-Brandt A, et al. Cognitive declines precede and predict functional declines in aging and Alzheimer's disease. *PLoS One*. 2013;8:e73645, http://dx.doi.org/10.1371/journal.pone.0073645.
36. Sanz CM, Hanaire H, Vellas BJ, et al. Diabetes mellitus as a modulator of functional impairment and decline in Alzheimer's disease. The Real.FR cohort. *Diab. Med*. 2012;29:541–548. http://dx.doi.org/10.1111/j.1464-5491.2011.03445.x.
37. Hölscher C. First clinical data of the neuroprotective effects of nasal insulin application in patients with Alzheimer's disease. *Alzheimers Dement*. 2014;10(1 Suppl):S33–S37, http://dx.doi.org/10.1016/j.jalz.2013.12.006.
38. Francis GJ, Martinez JA, Liu WQ, et al. Intranasal insulin prevents cognitive decline, cerebral atrophy and white matter changes in murine type I diabetic encephalopathy. *Brain*. 2008;131:3311–3334, http://dx.doi.org/10.1093/brain/awn288.
39. McClean PL, Hölscher C. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer's disease. *Neuropharmacology*. 2014;76:57–67, http://dx.doi.org/10.1016/j.Neuropharm.2013.08.005.
40. Tang J, Pei Y, Zhou G. When aging-onset diabetes is coming across with Alzheimer disease: comparable pathogenesis and therapy. *Exp Gerontol*. 2013;48:744–750, http://dx.doi.org/10.1016/j.exger.2013.04.013.
41. van Harten B, Oosterman J, Muslimovic D, et al. Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus. *Age Ageing*. 2007;36:164–170, http://dx.doi.org/10.1093/ageing/afl180.
42. Crane PK, Walker R, Larson EB. Glucose levels and risk of dementia. *N Engl J Med*. 2013;369:1863–1864, http://dx.doi.org/10.1056/NEJMc1311765.
43. Watson GS, Cholerton BA, Reger MA, et al. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry*. 2005;13:950–958, http://dx.doi.org/10.1176/appi.ajgp.13.11.950.

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