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Association of Dipeptidyl Peptidase-4 Inhibitor Use and Amyloid Burden in Diabetic Patients With AD-Related Cognitive Impairment

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Abstract

***Objectives*:** To investigate whether dipeptidyl peptidase-4 inhibitors (DPP-4i) have beneficial effects on amyloid aggregation and longitudinal cognitive outcome in diabetic Alzheimer's disease-related cognitive impairment (ADCI).

***Methods*:** We retrospectively reviewed 282 patients with ADCI who had positive scan of ^{18}F-florbetaben amyloid PET images were classified into three groups according to a prior diagnosis of diabetes and DPP-4i use: diabetic patients being treated with (ADCI-DPP-4i^{+}, n=70) or without DPP-4i (ADCI-DPP-4i^{-}, n=71), and non-diabetic patients (n=141). Multiple linear regression analyses were performed to determine inter-group differences in global and regional amyloid retention using standardized uptake value ratios calculated from cortical areas. We assessed the longitudinal changes in Mini-Mental State Examination (MMSE) score using a linear mixed model.

***Results*:** The ADCI-DPP-4i^{+} group had lower global amyloid burden than the ADCI-DPP-4i^{-} group (β = 0.075, SE = 0.024, p = 0.002) and the non-diabetic ADCI group (β = 0.054, SE = 0.021, p = 0.010) after adjusting for age, sex, education, cognitive status, and APOE ε4 carrier status. Additionally, the ADCI-DPP-4i^{+} group had lower regional amyloid burden in temporo-parietal areas than either the ADCI-DPP-4i^{-} group or the non-diabetic ADCI group. The ADCI-DPP-4i^{+} group showed a slower longitudinal decrease in MMSE score (β = 0.772, SE = 0.272, p = 0.005) and memory recall sub-score (β = 0.291, SE = 0.116, p = 0.012) than the ADCI-DPP-4i^{-} group.

***Conclusions*:** These findings suggest that DPP-4i use is associated with low amyloid burden and favorable long-term cognitive outcome in diabetic patients with ADCI.

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Alzheimer's disease (AD), the most common neurodegenerative disease, is closely linked to diabetes mellitus (DM).[1] Progressive loss of beta cell function and mass in patients with DM could result from toxic aggregates of islet amyloid polypeptide or amylin, which is closely linked to defects in the proteasome and autophagy.[2, 3] Additionally, ample evidence has suggested that there are common mechanisms between AD and DM such as insulin resistance, insulin growth factor signaling, inflammatory response, oxidative stress, amyloid beta (Aβ) formation, and neurofibrillary tangle formation.

Dipeptidyl peptidase-4 inhibitors (DPP-4i) are widely used hypoglycemic agents associated with a low risk of hypoglycemia and weight gain.[4] DPP-4i improve glucose metabolism by enhancing the bioavailability of active glucagon-like peptide-1 (GLP-1) by inhibiting its degradation. In addition to their glycemic properties, DPP-4i have neuroprotective properties via pleotropic effects, such as modulating prosurvival and anti-apoptotic signaling, inhibiting phosphorylation of toxic proteins, inhibiting neuroinflammation, and enhancing synaptic plasticity in experimental AD models.[5-7] Recent clinical studies showed that the use of DPP-4i was associated with a favorable cognitive outcome in elderly as well as patients with mild cognitive impairment (MCI) or AD.[8-10] However, previous clinical studies have major limitations in that they enrolled patients without imaging biomarkers or neuropathological confirmation of AD. Positron emission tomography (PET) using ligands binding to Aβ is regarded as a valuable technique for visualizing and quantifying the deposition of Aβ throughout the brain in living patients and has very high sensitivity for detecting AD pathology. [11, 12] In the present study, we hypothesized that treatment with DPP-4i may confer protective effects against Aβ retention in patients with AD-related cognitive impairment (ADCI). Therefore, we performed a comparative analysis of standardized uptake value ratios (SUVRs) calculated from cerebral cortical areas by using ^{18}F-florbetaben (^{18}F-FBB) Aβ PET

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imaging and longitudinal changes in cognitive parameters in diabetic and non-diabetic patients with ADCI depending on prior treatment with DPP-4i.

Methods

Participants

We retrospectively reviewed 584 patients (337 patients in the Severance Hospital and 147 patients in the Gangnam Severance Hospital) who visited our clinic for subjective symptoms of cognitive impairment and exhibited Aβ positivity on ^{18}F-FBB scan from June 2015 to May 2020. A detailed neuropsychological study is performed to assess the level of cognitive impairment in patients with cognitive complaints in Severance Hospital and Gangnam Severance Hospital, and FBB-PET scans were performed on those determined to have cognitive impairment after the neuropsychological study or those with complaints of gradual decline in memory function.[13] In the final cohort, we included the patients with diabetes who met the criteria of "Probable AD dementia with evidence of the AD pathophysiological process", "Prodromal AD (MCI due to AD – High likelihood)", and "Preclinical AD" according to NIA-AA guidelines.[14-16] Additionally, we excluded (1) patients without information regarding diabetic medication, (2) patients whose cognitive impairment was combined with or ascribed to other etiologies, such as multi-infarct dementia with large territorial infarction and dementia with Lewy bodies (DLB).[16] Finally, we enrolled 141 diabetic patients with ADCI. To determine the effects of DM itself on Aβ burden, we additionally enrolled 141 age-, sex-, education, and cognitive status-matched non-diabetic patients with ADCI. Thus, we classified 282 enrolled patients into three groups according to a prior diagnosis of diabetes and use of DPP-4i: diabetic patients being treated with (ADCI-DPP-4i^{+} group) or without DPP-4i (ADCI-DPP-4i^{-} group), and non-diabetic patients (non-diabetic ADCI group; figure 1). Cognitive status was categorized into non-dementia

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(preclinical and prodromal AD) and dementia (probable AD). The onset of diabetes was defined by patient-reported physician-diagnosed diabetes, initiation of antidiabetic medication or fasting plasma glucose >125 mg/dl or HbA1c ≥ 6.5% among individuals with no prior record of diabetes based on electronic medical records of Severance Hospital and Gangnam Severance Hospital.[17] A patient was included in the DPP-4i^{+} group when they received DPP-4i within the 6 months prior to the date of the ^{18}F-FBB PET scan. We also investigated other oral hypoglycemic agents and insulin in addition to DPP-4i. We investigated other antidiabetic drugs as well as the type of DPP-4i that patients were taking (linagliptin, n = 19; sitagliptin, n = 18; vildagliptin, n = 8; gemigliptin, n = 6; teneligliptin, n = 5; alogliptin, n = 4; saxagliptin, n = 4; anagliptin, n = 4; and evogliptin, n = 2). There was no diabetic patient with ADCI who was being treated with a GLP-1 agonist.

Standard protocol approvals, registrations, and patient consents

This study was approved by the Yonsei University Severance Hospital institutional review board, and the need for informed consent was waived because of the retrospective nature of the study.

Acquisition and visual assessment of ^{18}F-FBB scans

^{18}F-FBB PET scans were obtained using a Discovery 600 system (General Electric Healthcare, Milwaukee, MI, USA) in Severance Hospital and a Biograph mCT PET/CT scanner (Siemens Medical Solutions, Malvern, PA, USA) in Gangnam Severance Hospital. ^{18}F-FBB-PET images were acquired 90 min after administration of 300 MBq (8 mCi) FBB for 20 min. Images were acquired with a 256 × 256 matrix and reconstructed with an ordered-subsets expectation maximization algorithm in an iso-0.98-mm voxel size. Acquisition corrections included decay, attenuation, scatter, dead time, normalization, sensitivity

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calibrated using a dose calibrator, and random correction. Brain Aβ plaque load (BAPL) scores[18] were assessed based on visual ratings by an expert reader at each hospital (Professor at the Department of Nuclear Medicine in either Severance Hospital or Gangnam Severance Hospital) who was blinded to the clinical diagnosis. All enrolled patients had BAPL scores of 2 or 3 which were classified as Aβ positivity.

Quantitative analyses of ^{18}F-FBB scans

Quantitative PET image analysis requires an individual T1-weighted structural image to define patient-specific gray matter region. Because T1-weighted magnetic resonance imaging (MRI) data corresponding with the ^{18}F-FBB PET images were not available in a considerable number of enrolled patients, we created a PET template.[19] The PET template was created using 454 paired image sets of healthy controls that had both T1-weighted MRI and ^{18}F-FBB PET data. Each PET image was co-registered in the Nathan Kline Institute (NKI) brain template space using the deformation field between the corresponding T1 MRI and NKI template and affine transformation between each T1-weighted image and PET image. The PET template was built by averaging the transformed PET images in the same normalized space. Additionally, each T1-weighted image was segmented and parcellated following the Desikan-Killiany Atlas using Freesurfer 5.3 so that the parcellation mask of the PET template could also be defined.

^{18}F-FBB PET images were then co-registered to the PET template using nonlinear registration in Advanced Normalization Tools to obtain the affine transformation matrix and deformation field. Inverse transformation was performed to warp the parcellation mask from the standard space of the PET template to the native space of each PET image. The participant-specific mask image comprised 68 cortical and ten subcortical parcellated regions of the Desikan-Killiany Atlas.[20] SUVRs were calculated according to the ADNI Florbetaben

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PET processing performed by UC Berkley.[21] Regional SUVRs were calculated for the four predefined cortical regions of interest (ROIs) (frontal, lateral temporal, lateral parietal, anterior/posterior cingulate) by overlaying the participant-specific composite masks. The whole cerebellum was used as the reference region. In addition, global SUVRs were established for each participant by volume-weighted averaging across four cortical regions and dividing this by the reference region. The difference of global and regional SUVRs among the groups was used for the primary outcome measure. A global measure of SUVRs in each hemisphere was further assessed by extracting each ROI count.[22] Specifically, patients with ADCI who were finally selected in this study had composite Aβ retention above the threshold for Aβ positivity (global SUVRs > 1.08) (see also https://adni.bitbucket.io/reference/docs/UCBERKELEYFBB/UCBerkeley_FBB_Methods_04.11.19.pdf).

Acquisition of MR images and visual rating of medial temporal lobe atrophy (MTA) and white matter hyperintensities (WMHs)

Of the 282 enrolled patients, 276 (97.87%) patients underwent brain MRI, including coronal T1-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, using a 3.0-Tesla scanner (Achieva; Philips Medical System, Best, The Netherlands) at the Severance Hospital and another 3.0-Tesla scanner (Discovery MR750, GE Medical Systems, Milwaukee, WI) at the Gangnam Severance Hospital. Three patients underwent brain MRI, including coronal T1-weighted and FLAIR sequences, at other hospitals. Three-dimensional (3D) isotropic 3.0-Tesla T1-weighted images were available in 244 (86.52%) patients. For MTA rating, coronal images located just posterior to the amygdala in the area of the cerebral peduncles were used. The MTA visual rating scale was assessed by two neurologists (S.H.J. and J.H.J.) using the Scheltens scale.[23] The average MTA was investigated in the current study. The visual rating

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scale of WMHs was assessed by two neurologists (S.H.J. and J.H.J) using the Fazekas scale. Periventricular WMHs areas were classified as P1 (cap and band < 5 mm), P2 (5 mm ≤ cap or band < 10 mm), and P3 (10 mm ≤ cap or band); deep WMHs areas were classified as D1 (maximum diameter of deep white matter lesion < 10 mm), D2 (10 mm ≤ lesion < 25 mm), and D3 (≥ 25 mm). The inter-rater reliabilities of the MTA, periventricular WMHs and deep WMHs were high (intraclass correlation coefficients = 0.876, 0.887, and 0.923 respectively). If MTA or WMHs scores were discordant between the raters, the final score was determined by consensus.

Neuropsychological test

At baseline, 273 participants (96.81%) underwent a standardized neuropsychological battery called the Seoul Neuropsychological Screening Battery (SNSB),[24] which contains tests for attention/working memory, language, visuospatial function, memory, and frontal/executive function. Standardized z scores were available for all scorable tests based on age- and education-matched norms. We included following tests in analyses: the digit span forward and backward for the attention domain; the Korean version of the Boston Naming test for the language domain; copying item of the Rey-Osterrieth Complex Figure test (RCFT) for the visuospatial domain; immediate recall, 20-minute delayed recall, and recognition items of the RCFT and Seoul Verbal Learning Test for the memory domain; and the Controlled Oral Word Association Test for semantic (animal and supermarket) and phonemic fluency and Stroop color reading test for the frontal/executive domain. A composite score was calculated for each cognitive domain by dividing the sum of the *z* scores by the number of tests. The operational definition of cognitive impairment that we used was described in a previous study.[25] In addition, the Korean version of the Mini-Mental State Examination (MMSE) was used to assess general cognition.[26] The MMSE scores were divided into sub-scores for

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orientation, memory registration, memory recall, attention, language, and construction in longitudinal analyses. Cognitive status was defined based on the consensus between two neurologists and one neuropsychologist according to the evidence of abnormal activities of daily living (ADL), judged both clinically and on the basis of instrumental ADL scales.[27, 28]

Longitudinal assessment of the changes in MMSE score and sub-score over time

Of 141 diabetic patients with ADCI, exclusion criteria in the longitudinal analysis were as follows: (1) patients whose longitudinal MMSE data were not available, (2) patients who discontinued DPP-4i during follow-up, and (3) patients who initiated DPP-4i during follow-up. Thus, 108 were included in the final longitudinal analysis after exclusion (figure 1). The median follow-up duration was 30 months (range: 12–64 months). A linear mixed-effect model was used to compare the rate of longitudinal changes in MMSE score between groups after adjusting for age at ^{18}F-FBB scan, sex, education, cognitive status, APOE ε4 carrier status and global SUVRs. The group effect on the longitudinal MMSE change over time was tested with a group × time interaction term. Among MMSE sub-scores, because the score of memory recall had excess zeros and overdispersion, mixed-effects zero-inflated quasi-Poisson regressions were used to minimize potential floor effects.

Statistical analyses

To compare the baseline demographic characteristics among the groups, one-way ANOVA with post-hoc false discovery rate (FDR) correction was used for continuous variables, and Pearson's χ^2 tests or Fisher exact tests were used for categorical variables. Independent sample t-test was used to compare continuous variables between the diabetic groups. To compare the SUVRs of each cortical region and the composite scores of each cognitive domain among the groups, the FDR method for multiple comparisons was used. Multivariate

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linear regression analysis was used to determine the independent effects of DPP-4i after adjusting for age at ^{18}F-FBB scan, sex, education, cognitive status, and APOE ε4 carrier status. A mixed-effect model was used to compare the longitudinal MMSE score and sub-score changes between the diabetic groups. Statistical analyses were performed using SPSS (version 25.0; IBM Corporation, Armonk, NY, USA) and R (v4.0, http://www.r-project.org/). We also presented *q* values that are FDR-corrected *p* values for multiple comparisons. Results with *p*- or *q*-value < 0.05 were considered statistically significant.

Data availability

The de-identified data that support the findings of this study are available from the authors upon reasonable request.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the non-diabetic ADCI (n = 141), ADCI-DPP-4i^{-} (n = 71) and ADCI-DPP-4i^{+} (n = 70) groups enrolled in this study are summarized in table 1. Age at ^{18}F-FBB scan, age at MRI scan, years of education, baseline MMSE score, CDR-SOB, and body mass index did not differ among the groups. APOE ε4 carrier was more prevalent in the non-diabetic ADCI group than the ADCI-DPP-4i^{+} group. The proportion of hypertension was higher in the ADCI-DPP-4i^{-} and ADCI-DPP-4i^{+} groups than in the non-diabetic ADCI group. Vascular risk factors including hypertension, dyslipidemia, and cardiac disease were comparable between the ADCI-DPP-4i^{-} and ADCI-DPP-4i^{+} groups. The co-prescription of other antidiabetic drugs, such as metformin, sulfonylurea, thiazolidinedione, α-glucosidase, and insulin, did not differ significantly between the diabetic groups. Fasting glucose tended to be higher in the ADCI-DPP-4i^{+} group than in the ADCI-DPP-4i^{-} group.

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HbA1c in the ADCI-DPP-4i^{+} group was significantly higher than that in the ADCI-DPP-4i^{-} group. The visual rating of MTA, periventricular WMHs, and deep WMHs did not differ between groups. Sixty patients (42.6%) in the non-diabetic ADCI group, 32 patients (45.1%) in the ADCI-DPP-4i^{-} group, and 29 patients (41.4%) in the ADCI-DPP-4i^{+} group were probable AD. The frequency of non-dementia (preclinical and prodromal AD) and dementia (probable AD) was comparable among the groups. The mean duration of DPP-4i use prior to ^{18}F-FBB scan was 4.01 ± 2.34 years in the ADCI-DPP-4i^{+} group.

Comparison of Aβ burden between the groups

The composite SUVRs and that for each cortical region are shown in figure 2A. The ADCI-DPP-4i^{+} group had significantly lower global SUVRs (1.33 ± 0.14 vs. 1.41 ± 0.16, p = 0.001, q = 0.006) and lower SUVRs in the frontal (1.33 ± 0.16 vs. 1.41 ± 0.17, p = 0.002, q = 0.006), lateral parietal (1.34 ± 0.14 vs. 1.42 ± 0.17, p = 0.002, q = 0.006), lateral temporal (1.33 ± 0.14 vs. 1.41 ± 0.16, p = 0.002, q = 0.006), and anterior cingulate/posterior cingulate cortices (1.43 ± 0.21 vs. 1.53 ± 0.20, p = 0.002, q = 0.006) than those in the ADCI-DPP-4i^{-} group. Additionally, the ADCI-DPP-4i^{+} group had lower composite (1.33 ± 0.14 vs. 1.39 ± 0.13, p = 0.009, q = 0.020) and lateral temporal SUVRs (1.33 ± 0.14 vs. 1.41 ± 0.14, p < 0.001, q = 0.002) compared to the non-diabetic ADCI group (figure 2A). Multivariate linear regression analyses revealed that the ADCI-DPP-4i^{+} group was significantly and independently associated with lower Aβ burden globally (β = 0.075, SE = 0.024, p = 0.002, q = 0.003) and in all four regional cortices (frontal, β = 0.076, SE = 0.025, p = 0.003, q = 0.003; lateral parietal, β = 0.072, SE = 0.023, p = 0.002, q = 0.003; lateral temporal, β = 0.074, SE = 0.024, p = 0.003, q = 0.003; anterior/posterior cingulate, β = 0.099, SE = 0.032, p = 0.002, q = 0.003) compared to the ADCI-DPP-4i^{-} group after adjusting for age at ^{18}F-FBB scan, sex, education, cognitive status, and APOE ε4 carrier status (table 2). Moreover, the ADCI-DPP-4i^{+} group

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had lower Aβ burden globally (β = 0.054, SE = 0.021, p = 0.010, q = 0.026) and in two regional cortices (lateral parietal, β = -0.046, SE = 0.021, p = 0.026, q = 0.044; lateral temporal, β = -0.083, SE = 0.021, p < 0.001, q = 0.001) than the non-diabetic ADCI group. Next, we examined the whole-brain distribution of ^{18}F-FBB load overlaid on brain surfaces in the non-diabetic ADCI, ADCI-DPP-4i^{+} and ADCI-DPP-4i^{-} groups. As expected, SUVRs in the frontal, lateral temporal, lateral parietal, and anterior/posterior cingulate cortices had noticeably higher values than other cortical areas in all three groups (figure 2B). A between-group comparison revealed that the SUVRs of diffuse cortical regions in the ADCI-DPP-4i^{+} group were significantly lower than those in the ADCI-DPP-4i^{-} group, which was significantly contrasting in the frontal, lateral temporal, lateral parietal, and anterior/posterior cingulate areas. Also, the SUVRs of frontal, temporal, and parietal areas in the ADCI-DPP-4i^{+} group were significantly lower than those in the non-diabetic ADCI group (figure 2C).

Longitudinal assessment of the changes in MMSE score between the groups

The 108 diabetic patients with ADCI (ADCI-DPP-4i^{-}, n = 56, follow-up duration = 2.35 ± 1.00; ADCI-DPP-4i^{+}, n = 52, follow-up duration = 2.20 ± 1.05) who had at least two MMSE scores with a 1-year interval had similar demographic characteristics and SUVRs as all enrolled patients (table 3). The mean duration of DPP-4i use prior to baseline MMSE was 3.38 ± 2.21 years in the ADCI-DPP-4i^{+} group. There was a significant positive value for the group × time interaction term in the linear mixed model of MMSE total score (β = 0.772, SE = 0.272, p = 0.005, q = 0.034) after adjusting for age at ^{18}F-FBB scan, sex, education, cognitive status, APOE ε4 carrier status, group, time, and group × time, indicating that the longitudinal MMSE score decrement per a year was approximately 0.77 smaller in the ADCI-DPP-4i^{+} group than in the ADCI-DPP-4i^{-} group (table 3 and figure 3). Among the MMSE sub-scores, the group × time interaction term was significant only for the memory recall sub-

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score (β = 0.291, SE = 0.116, p = 0.012, q = 0.044) after adjusting for age at ^{18}F-FBB scan, sex, education, cognitive status, APOE ε4 carrier status, group, time, and group × time in the mixed-effects zero-inflated quasi-Poisson regression (table 4). We further investigated the effect modification by adjusting for the effect of Aβ on cognition. The global SUVRs × time interaction term was significant for the MMSE total score (β = -2.617, SE = 0.895, p = 0.004, q = 0.013) and orientation sub-score (β = -1.253, SE = 0.427, p = 0.004, q = 0.013) after adjusting for age, sex, education, cognitive status, APOE ε4 carrier status, global SUVRs, and global SUVRs × time. In the two-way interaction model, the DPP-4i × time interaction term was no longer significant for MMSE total score (β = 0.588, SE = 0.281, p = 0.038, q = 0.119) and memory recall sub-score (β = 0.258, SE = 0.122, p = 0.034, q = 0.119) after addition of the global SUVRs × time interaction term (table 4), indicating that DPP-4i's effect on longitudinal cognition may be indirect through Aβ burden.

Discussion

In this study, we investigated the effects of DPP-4i on baseline Aβ burden and the longitudinal course of cognition in patients with ADCI. The major findings are as follows: (1) diabetic patients with ADCI treated with DPP-4i^{+} had significantly lower Aβ burden than those treated without DPP-4i^{-} and those without diabetes; and (2) the ADCI-DPP-4i^{+} group had a slower longitudinal decline in cognitive performance than the ADCI-DPP-4i^{-} group. These findings suggest that DPP-4i may have beneficial effects on Aβ burden and long-term cognitive outcomes in diabetic patients with ADCI.

The beneficial effects of DPP-4i have been demonstrated in several preclinical models of AD. DPP-4i prohibits Aβ-induced neuronal cell apoptosis via DPP-4i's own effects or endogenous GLP-1 elevation in cellular models.[29-31] *In vivo* studies also support that DPP-4i restore the

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core neurodegenerative processes in AD models. Kosaraju et al. reported that vildagliptin, saxagliptin or linagliptin treatment led to decreased Aβ, total tau, and phosphylated tau levels in the hippocampus, and also suppressed neuroinflammation, which was accompanied by improvement on cognitive performance.[32-34] Unlike the GLP-1 receptor agonist, DPP-4i cannot cross the blood-brain barrier.[35, 36] Thus, the beneficial effects of DPP-4i may be indirectly conferred through an increase in the levels of GLP-1 in the peripheral blood, which can cross the blood-brain barrier.[37, 38]

The uniqueness of the present study is that the diagnosis of all enrolled patients was supported by an ^{18}F-FBB PET scan, which is a widely used Aβ imaging biomarker. We found that those of the ADCI-DPP-4i^{+} group had significantly lower global and regional Aβ SUVRs than the ADCI-DPP-4i^{-} group. This is the first study demonstrating that prior treatment with DPP-4i is associated with low Aβ burden in patients with ADCI. Interestingly, the present study showed that relative to the ADCI-DPP-4i^{-} group, the ADCI-DPP-4i^{+} group exhibited lower Aβ load in the frontal, lateral parietal, lateral temporal, and anterior/posterior cingulate cortices, which are the main structures involved in AD. Moreover, the ROI-based group comparison of whole brain also demonstrated that cortical Aβ burden was diffusely more attenuated in the ADCI-DPP-4i^{+} group than in the ADCI-DPP-4i^{-} group. Given that Aβ accumulation already starts in the presymptomatic stage of AD from the cingulate and frontal cortices to the parietal and temporal cortices,[39-43] it can be inferred that DPP-4i may modulate Aβ accumulation in the process of AD. Although ample evidence suggests that DM increases the future risk of AD,[44, 45] the effect of DM on Aβ burden is controversial. Moran et al. showed that the presence of DM was not associated with Aβ burden using Alzheimer's Disease Neuroimaging Initiative data.[46] Tomita et al. also reported that the degree and extent of Aβ deposition did not differ according to the presence of DM in patients with AD.[47] Our

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result is consistent with previous studies showing that baseline Aβ burden was similar in patients with ADCI regardless of the presence of DM. Interestingly, the present study showed that the ADCI-DPP-4i^{+} group had lower global Aβ burden than the non-diabetic ADCI group. This result raises the possibility that the beneficial effects of DPP-4i on Aβ burden may extend its role into non-diabetic patients with ADCI. To demonstrate the neuroprotective properties of DPP-4i, more definitive data are needed from a randomized study.

In this study, we found that the ADCI-DPP-4i^{+} group showed slower longitudinal decline in the MMSE score than that in the ADCI-DPP-4i^{-} group. To date, there have been some retrospective longitudinal studies supporting that ADCI-DPP-4i has protective effects on cognitive outcomes in patients with MCI or AD. Isik et al. reported that sitagliptin therapy led to improvement of cognitive function in diabetic patients without AD, as well as those with AD.[8] A recent study suggested that DPP-4i would have beneficial effects on cognitive outcomes in diabetic patients with AD, and APOE ε4 genotype may modify the relationship between the use of DPP-4i and memory decline in cognitively normal elderly.[10] In the present study, the ADCI-DPP-4i^{+} group showed a significantly blunted decline in global cognition. In terms of the MMSE sub-scores, the mixed-effect models showed that only the memory recall sub-score, which is the mainly affected sub-score in AD pathology, showed significantly slower progression in the DPP-4i^{+} group. In further analyses, baseline Aβ burden negatively affected the rate of cognitive decline, which is in line with previous studies.[48] However, when further considering the effect of Aβ burden on cognitive decline, DPP-4i treatment no longer exhibited beneficial effects on cognitive decline. It is plausible that along with the association between DPP-4i use and baseline Aβ retention, the properties of DPP-4i on long-term cognition may be an indirect effect of baseline Aβ burden. However, as sequential Aβ accumulation data were not available, the exact mechanism underlying the association

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between DPP-4i use and slow MMSE decline cannot be determined in this study. Further randomized clinical trials are needed to clearly uncover the mechanisms of the beneficial effects of DPP-4i with respect to the progression of AD.

Our study has some limitations. First, due to the nature of this retrospective cross-sectional study, causal relationships should be demonstrated in other longitudinal comparative studies using sequential Aβ imaging. Additionally, the effect of sugar control was not included in the analysis due to unavailable sequential HbA1c data and missing baseline HbA1c data. Second, the use of DPP-4i can induce selection bias because there is a preference for DPP-4i in diabetic patients who are vulnerable to hypoglycemia such as elderly patients,[49] despite the lack of specific limitations of DPP-4i use according to the guidelines. Moreover, considering that DPP-4i are generally used as additive hypoglycemic drugs when a patient's sugar control is insufficient for metformin use, higher fasting sugar and HbA1c levels may reflect severe insulin resistance. Further studies on euglycemic patients are necessary to control the effect of peripheral insulin resistance. Third, although the MMSE, which is regarded as an effective longitudinal monitoring tool, was used to analyze the longitudinal outcomes of global cognition,[50] more precise tests, such as neuropsychological batteries, may be more appropriate to evaluate cognitive function. Finally, because we enrolled some patients who did not have three-dimensional isotropic 3T T1-weighted structural MRI data, we acquired SUVRs using an individually adaptive template derived from Aβ PET and this method can be less accurate than the classical method.

In conclusion, the present study demonstrated that DPP-4i use is associated with low Aβ burden and favorable long-term cognitive outcome in diabetic patients with ADCI.

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Appendix 1. Authors

Name	Location	Contribution
Seong Ho Jeong, MD	Yonsei University College of Medicine; Sanggye Paik Hospital, Inje University College of Medicine	Design and conceptualized study; analyzed data; major role in the acquisition of data; interpreted the data; drafted the manuscript for intellectual content
Hye Ryun Kim, PhD	Global Health Technology Research Center, Korea University	Analyzed data; major role in the acquisition of data; interpreted the data; drafted the manuscript for intellectual content
Jeonghun Kim, PhD	Medical & Health Device Division, Korea Testing Laboratory	Interpreted the data; revised the manuscript for intellectual content
Hankyeol Kim, MD	Yonsei University College of Medicine	Major role in the acquisition of data; analyzed data; revised the manuscript for intellectual content
Namki Hong, MD	Yonsei University College of Medicine	Interpreted the data; revised the manuscript for intellectual content
Jin Ho Jung, MD	Inje University Busan Paik Hospital	Interpreted the data; revised the manuscript for intellectual content
Kyoungwon Baik, MD	Yonsei University College of Medicine	Interpreted the data; revised the manuscript for intellectual content
Hanna Cho, MD, PhD	Yonsei University	Interpreted the data; revised the manuscript

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	College of Medicine	for intellectual content
Chul Hyoung Lyoo, MD, PhD	Yonsei University College of Medicine	Interpreted the data; revised the manuscript for intellectual content
Byoung Seok Ye, MD, PhD	Yonsei University College of Medicine	Interpreted the data; revised the manuscript for intellectual content
Young H. Sohn, MD, PhD	Yonsei University College of Medicine	Interpreted the data; revised the manuscript for intellectual content
Joon-Kyung Seong, PhD	School of Biomedical Engineering, Korea University	Major role in the acquisition of data; analyzed data; revised the manuscript for intellectual content
Phil Hyu Lee, MD, PhD	Yonsei University College of Medicine	Design and conceptualized study; interpreted data; drafted the manuscript for intellectual content

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Table 1. Baseline demographic characteristics

		Non-diabetic ADCI (n=141)	ADCI-DPP-4i^{-} (n=71)	ADCI-DPP-4i^{+}(n=70)	*p*
Age at ^{18}F-FBB scan		76.26 ± 6.49	76.25 ± 6.01	77.35 ± 6.04	0.451
Age at MRI scan		76.13 ± 6.55	75.89 ± 6.01	76.94 ± 6.24	0.599
Female		84 (59.6%)	46 (64.8%)	40 (57.1%)	0.631
APOE ε4 carrier		76 (56.3%)	27 (38.0%)	24 (34.3%)	0.025[b]
Body mass index (kg/m2)		23.10 ± 3.18	24.03 ± 3.48	23.83 ± 3.61	0.111
Education, y		10.52 ± 5.20	9.72 ± 5.03	10.06 ± 5.65	0.562
MMSE		22.55 ± 4.09	22.03 ± 4.48	22.34 ± 4.26	0.702
CDR_SOB		2.70 ± 2.24	3.23 ± 2.59	2.82 ± 1.71	0.263
Cognitive status[c]					0.902
Non-dementia	Preclinical AD	4 (2.8%)	3 (4.2%)	1 (1.4%)	
	Prodromal AD	77 (54.6%)	36 (50.0%)	40 (57.1%)	
Dementia	Probable AD	60 (42.6%)	32 (45.1%)	29 (41.4%)	
Cognitive domain[d]					
Attention		-0.18 ± 0.87	-0.39 ± 0.78	-0.18 ± 0.84	0.192
Language		-0.92 ± 1.31	-1.43 ± 1.94	-1.31 ± 1.58	0.050
Visuospatial		-0.92 ± 1.89	-1.37 ± 2.05	-1.13 ± 1.78	0.275
Memory		-1.37 ± 0.73	-1.25 ± 0.87	-1.35 ± 0.77	0.567
Frontal/executive		-0.84 ± 0.77	-1.10 ± 0.90	-1.12 ± 0.74	0.017
Visual rating of MRI scan					
MTA		1.82 ± 0.92	2.07 ± 0.68	2.11 ± 0.80	0.030[b]
Periventricular WMHs		1.52 ± 0.75	1.77 ± 0.80	1.64 ± 0.73	0.078
Deep WMHs		1.42 ± 0.69	1.55 ± 0.77	1.39 ± 0.65	0.282
Visual rating of ^{18}F-FBB scan					0.421
BAPL 2		9 (6.4%)	5 (7.0%)	8 (11.4%)	
BAPL 3		132 (93.6%)	66 (93.0%)	62 (88.6%)	
Vascular risk factors					
Hypertension		70 (49.6%)	48 (67.6%)	50 (71.4%)	0.003[a, b]
Dyslipidemia		38 (27.0%)	26 (36.6%)	24 (34.3%)	0.291
Cardiac disease		22 (15.6%)	18 (25.4%)	17 (24.3%)	0.154
DM duration, y		-	15.39 ± 11.37	16.44 ± 8.78	0.541
Fasting glucose (mg/dL)		-	125.60 ± 31.6	135.80 ± 36.08	0.086
HbA1c (%)		-	6.84 ± 0.96	7.30 ± 1.07	0.012
DPP-4i duration prior to FBB scan		-	4.01 ± 2.34	-	NA
Antidiabetic drugs		-			
Metformin		-	51 (71.8%)	54 (77.1%)	0.470
Sulfonylurea		-	25 (35.2%)	32 (45.7%)	0.204

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Thiazolidinedione	-	9 (12.7%)	9 (12.9%)	0.974
α-glucosidase inhibitors	-	3 (4.2%)	2 (2.9%)	>0.999
Insulin	-	12 (16.9%)	9 (12.9%)	0.500

Values are expressed as mean ± standard deviation or number (percentage); *p*-values are the results of the independent sample t-test, χ^2 test. or Fisher exact test, as appropriate.

[a] Significantly different in comparison between non-diabetic ADCI and ADCI-DPP-4i$^-$

[b] Significantly different in comparison between non-diabetic ADCI and ADCI-DPP-4i$^+$

[c] A chi-square test was performed to compare the distributions of non-dementia and dementia. There was no difference in distribution among the groups (non-diabetic ADCI vs. ADCI-DPP-4i$^-$, χ^2 = 0.122, p = 0.727; non-diabetic ADCI vs. ADCI-DPP-4i$^+$, χ^2 = 0.024, p = 0.876; ADCI-DPP-4i$^-$ vs. ADCI-DPP-4i$^+$, χ^2 = 0.190, p = 0.663).

[d] No difference between the groups after multiple comparison corrections for 15 comparison (5 cognitive domain in 3 groups) using false discovery rate method

Abbreviations: AD = Alzheimer's disease; ADCI = AD-related cognitive impairment; BAPL = Brain amyloid plaque load; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; DM = diabetes mellitus; DPP-4i = dipeptidyl peptidase-4 inhibitors; FBB = florbetaben; MMSE = mini-mental status examination; MTA = medial temporal lobe atrophy; SUVRs = standardized uptake value ratios; WMHs, white matter hyperintensities.

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Table 2. Multiple linear regression analysis of global and regional amyloid retention

		Frontal SUVRs	Lateral Parietal SUVRs	Lateral Temporal SUVRs	Anterior/Posterior Cingulate SUVRs	Global SUVRs
		F=2.69, p=0.022	F=3.24, p=0.003	F=3.94, p<0.001	F=2.98, p=0.005	F=4.33, p<0.001
ADCI-DPP-4i^{+}	-	Ref.	Ref.	Ref.	Ref.	Ref.
ADCI-DPP-4i^{-}	β	0.076	0.072	0.074	0.099	0.075
	SE	0.025	0.023	0.024	0.032	0.024
	Beta	0.212	0.210	0.215	0.221	0.224
	p	0.003	0.002	0.003	0.002	0.002
	q[a]	0.003	0.003	0.003	0.003	0.003
Non-diabetic ADCI	β	0.044	0.046	0.083	0.055	0.054
	SE	0.022	0.021	0.021	0.028	0.021
	Beta	0.142	0.155	0.279	0.141	0.185
	p	0.051	0.026	<0.001	0.054	0.010
	q[a]	0.054	0.044	0.001	0.054	0.026

Results of multivariate linear regression analysis for the global and regional SUVRs after controlling for age at ^{18}F-FBB scan, sex, education, cognitive status and APOE ε4 carrier status.

[a] *q*-values indicate FDR-corrected *p*-values for five models of global and regional SUVRs using false discovery rate method

Abbreviations: ADCI = Alzheimer's disease-related cognitive impairment; β = unstandardized regression coefficient; Beta = standardized regression coefficient; DPP-4i = dipeptidyl peptidase-4 inhibitors; SE = standard error; SUVRs = standardized uptake value ratios.

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Table 3. Baseline demographic characteristics of patients with ADCI who were included in the longitudinal analysis

		ADCI-DPP-4i^{-} (n=56)	ADCI-DPP-4i^{+}(n=52)	*p*
Age at ^{18}F-FBB scan		75.89 ± 6.34	78.01 ± 5.85	0.076
Age at MRI scan		75.68 ± 6.35	77.58 ± 6.14	0.118
Female		39 (69.6%)	29 (55.8%)	0.136
APOE ε4 carrier		20 (35.7%)	19 (36.5%)	0.981
Body mass index (kg/m2)		23.36 ± 2.97	23.61 ± 3.53	0.690
Education, y		9.59 ± 4.81	9.46 ± 5.90	0.902
MMSE		22.43 ± 4.30	22.15 ± 4.40	0.744
CDR_SOB		3.25 ± 2.55	2.73 ± 1.66	0.213
Cognitive status				0.379[a]
Non-dementia	Preclinical AD	3 (5.4%)	1 (1.9%)	
	Prodromal AD	28 (50.0%)	32 (61.5%)	
Dementia	Probable AD	25 (44.6%)	19 (36.5%)	
Cognitive domain				
Attention		-0.40 ± 0.81	-0.13 ± 0.80	0.479[b]
Language		-1.50 ± 2.06	-1.17 ± 1.67	0.859[b]
Visuospatial		-1.17 ± 2.04	-0.94 ± 1.49	0.859[b]
Memory		-1.24 ± 0.88	-1.26 ± 0.80	0.997[b]
Frontal/executive		-1.07 ± 0.88	-1.07 ± 0.71	0.997[b]
Vascular risk factors				
Hypertension		37 (66.1%)	38 (73.1%)	0.430
Dyslipidemia		20 (35.7%)	15 (28.8%)	0.446
Cardiac disease		13 (23.2%)	14 (26.9%)	0.657
DM duration, y		14.16 ± 11.01	17.12 ± 9.16	0.133
Fasting glucose (mg/dL)		125.36 ± 31.09	133.58 ± 31.75	0.086
HbA1c (%)		6.79 ± 0.81	7.25 ± 1.04	0.012
DPP-4i duration prior to baseline MMSE		3.38 ± 2.21	-	
Anti-diabetic drugs				
Metformin		42 (75.0%)	38 (73.1%)	0.820
Sulfonylurea		18 (32.1%)	21 (40.4%)	0.373
Thiazolidinedione		7 (12.5%)	7 (13.5%)	0.882
α-glucosidase inhibitors		1 (1.8%)	2 (3.8%)	0.608
Insulin		7 (12.5%)	8 (15.4%)	0.665
Visual rating of MRI scan				

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MTA	2.04 ± 0.69	2.26 ± 0.72	0.096
Periventricular WMHs	1.77 ± 0.81	1.71 ± 0.76	0.684
Deep WMHs	1.54 ± 0.79	1.45 ± 0.61	0.533
Visual rating of FBB scan			0.654
BAPL 2	5 (8.9%)	6 (11.5%)	
BAPL 3	51 (91.1%)	46 (88.5%)	
Amyloid retention			
Frontal SUVRs	1.40 ± 0.17	1.33 ± 0.16	0.037[b]
Lateral parietal SUVRs	1.42 ± 0.17	1.35 ± 0.14	0.028[b]
Lateral temporal SUVRs	1.41 ± 0.17	1.33 ± 0.14	0.028[b]
Anterior/posterior cingulate SUVRs	1.52 ± 0.19	1.44 ± 0.20	0.035[b]
Global SUVRs	1.41 ± 0.16	1.34 ± 0.14	0.028[b]

Values are expressed as mean ± standard deviation or number (percentage); *p*-values are the results of the independent sample t-test, χ^2 test. or Fisher exact test, as appropriate.

[a] A chi-square test was performed to compare the distributions of non-dementia and dementia. There was no difference in distribution between the groups ($\chi^2 = 0.734$, $p = 0.392$)

[b] *q*-values (FDR-corrected *p*-values) after multiple comparison correction using the false discovery rate method for five variables.

Abbreviations: AD = Alzheimer's disease; ADCI = AD-related cognitive impairment; BAPL = Brain amyloid plaque load; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; DM = diabetes mellitus; DPP-4i = dipeptidyl peptidase-4 inhibitors; FBB = florbetaben; FDR = false discovery rate; MMSE = mini-mental status examination; MTA = medial temporal lobe atrophy; SUVRs = standardized uptake value ratios; WMHs, white matter hyperintensities.

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Table 4. Longitudinal models for DPP-4i and amyloid retention predicting MMSE total and sub-scores change over time

Model	Variables		MMSE total	Orientation	Calculation	Registration	Recall	Language	Pentagon
I	DPP-4i × time	β	0.772	0.130	0.222	0.012	0.291	0.135	0.076
		SEM	0.272	0.132	0.098	0.045	0.116	0.107	0.108
		p	0.005	0.324	0.025	0.782	0.012	0.210	0.480
		q[a]	0.034	0.453	0.057	0.782	0.044	0.367	0.560
II	Aβ × time	β	-2.617	-1.253	-0.610	-0.202	-0.520	-0.357	-0.052
		SEM	0.895	0.427	0.325	0.147	0.365	0.351	0.342
		p	0.004	0.004	0.062	0.891	0.154	0.310	0.880
		q[a]	0.013	0.013	0.145	0.891	0.255	0.434	0.891
III.	DPP-4i × time	β	0.588	0.019	0.185	0.012	0.258	0.112	0.075
		SEM	0.281	0.136	0.102	0.047	0.122	0.112	0.112
		p	0.038	0.887	0.072	0.796	0.034	0.316	0.503
		q[a]	0.119	0.887	0.167	0.887	0.119	0.553	0.704
	Aβ × time	β	-2.061	-1.236	-0.432	-0.007	-0.295	-0.253	0.014
		SEM	0.927	0.447	0.337	0.153	0.383	0.367	0.358
		p	0.027	0.006	0.201	0.966	0.441	0.491	0.968
		q[a]	0.132	0.043	0.468	0.968	0.688	0.688	0.968

All mixed effect models included age at ^{18}F-FBB scan, sex, education, cognitive status, APOE ε4 carrier status as covariates, predicting MMSE score change.

[a] *q*-values indicate FDR-corrected *p*-values for seven models of MMSE total and sub-scores using false discovery rate method.

Abbreviations: β = unstandardized coefficient; Aβ = global standardized uptake value ratios; DPP-4i = dipeptidyl peptidase-4 inhibitors; FBB = florbetaben; FDR = false discovery rate; SEM = standard error of the mean

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FIGURE LEGENDS

Figure 1. Flowchart of participants

Abbreviation: ADCI = Alzheimer's disease-related cognitive impairment; DM = diabetes mellitus; DPP-4i = dipeptidyl peptidase-4 inhibitors; FBB = florbetaben; MMSE = mini-mental status examination; SUVRs = standardized uptake value ratios.

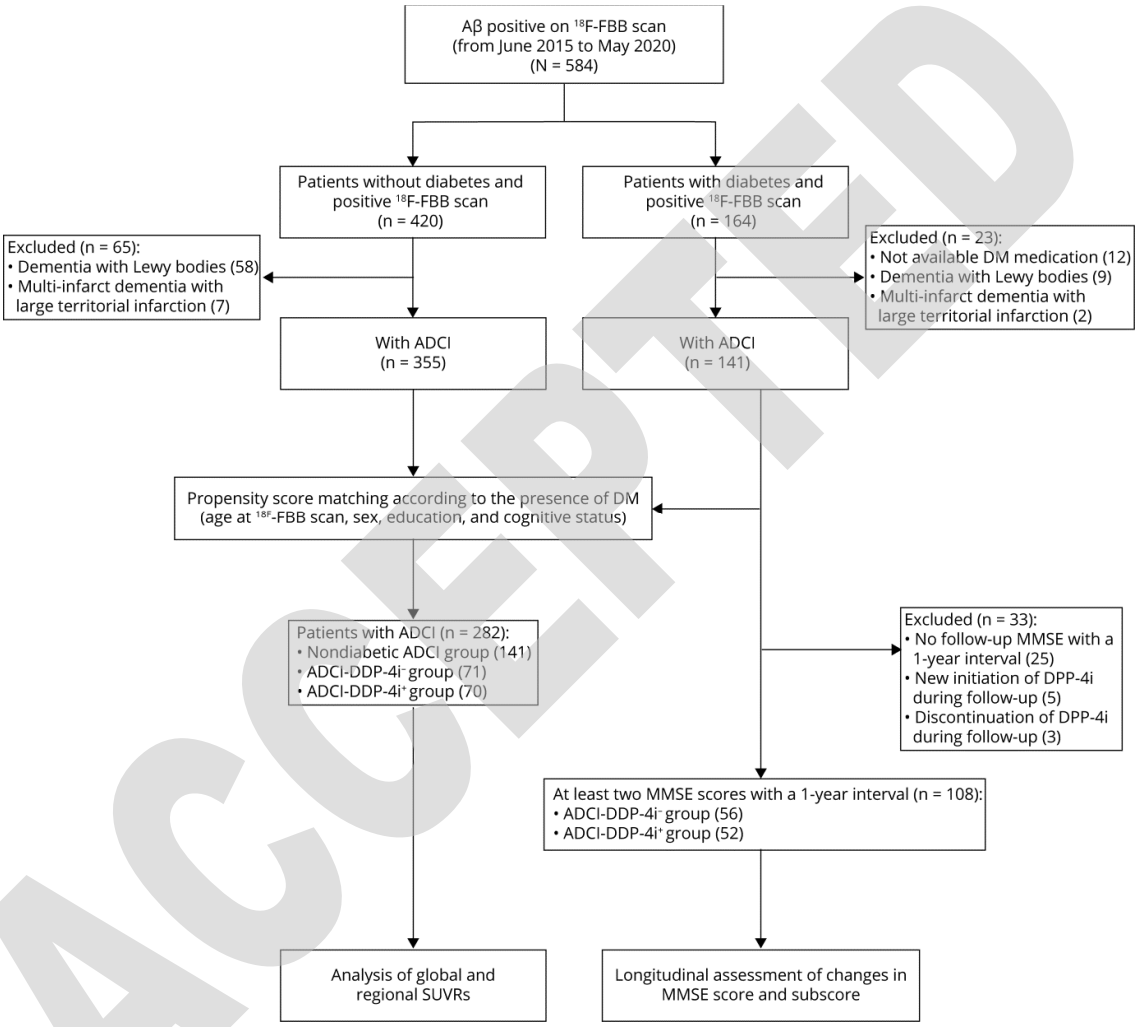

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Figure 2. Group comparison of amyloid retention

(A) Rain-cloud plots of global and regional amyloid retention using SUVRs. *0.05 ≤ *q*-value (FDR corrected *p*-value) < 0.1, **0.01 ≤ *q*-value < 0.05, ***q-value < 0.01. (B) Patterns of amyloid deposition in each group. (C) Group comparison among the groups was shown as T-maps after correction from multiple comparisons (*q*-value < 0.05). Red = larger amyloid SUVRs in latter group, green = smaller amyloid SUVRs in latter group.

Abbreviation: ADCI = Alzheimer's disease-related cognitive impairment; DPP-4i = dipeptidyl peptidase-4 inhibitors; FDR = false discovery rate; SUVRs, standardized uptake value ratios

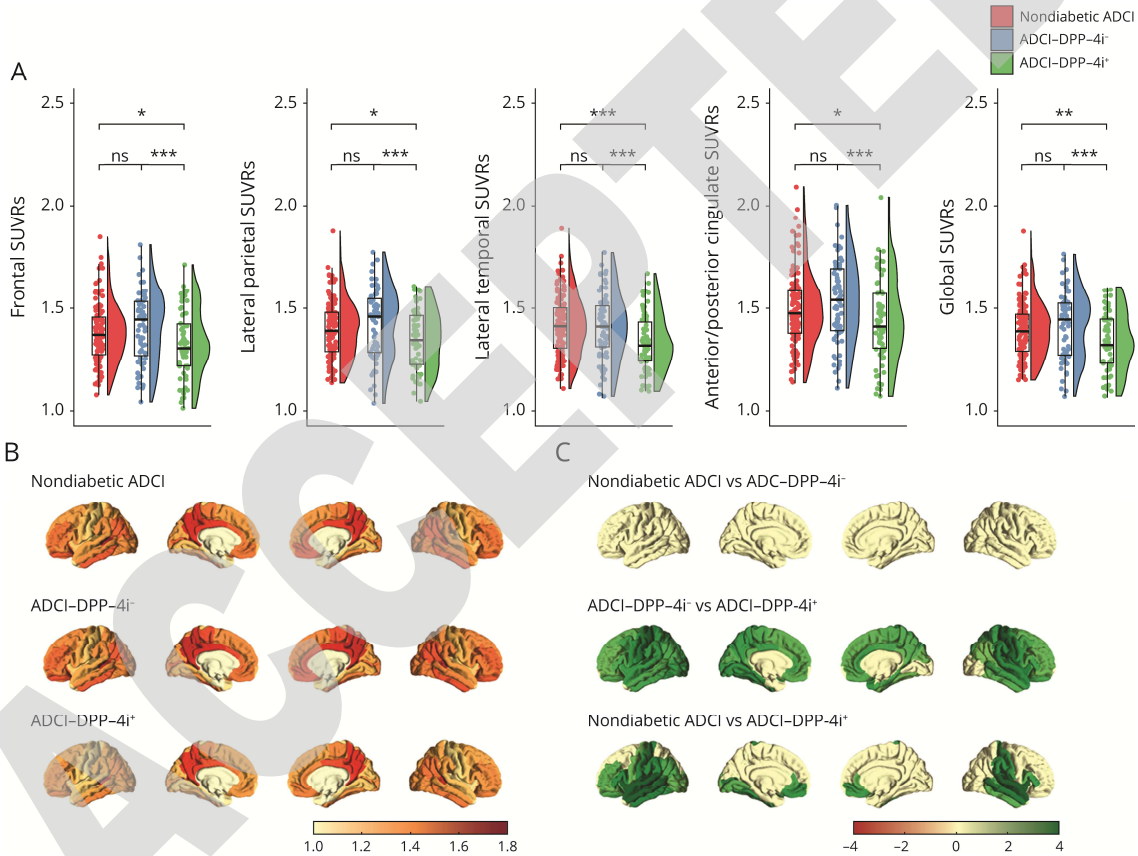

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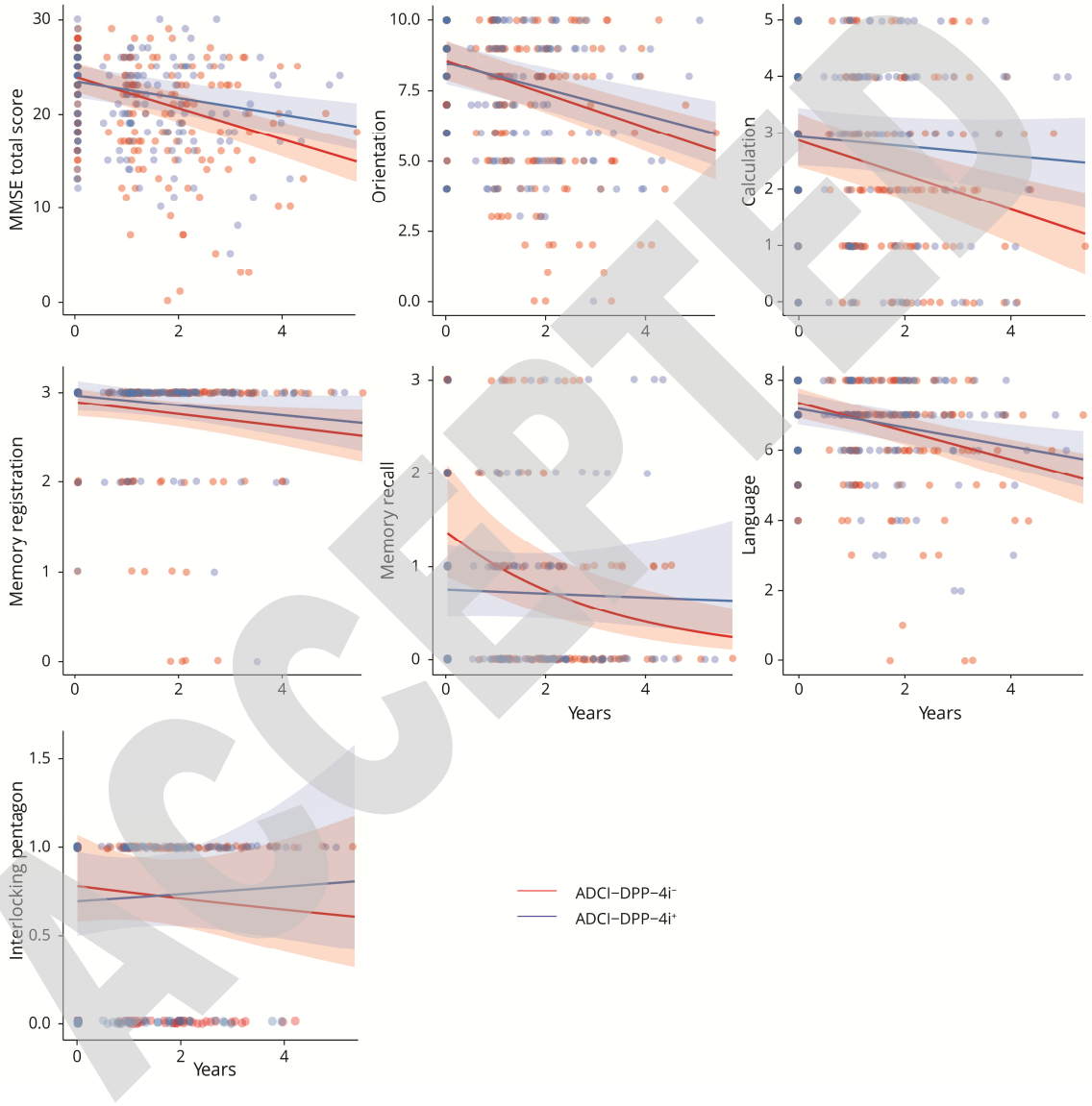
Figure 3. Association between DPP-4i use and MMSE total and sub-scores over time

The ADCI-DPP-4i^{+} group had significantly slower decline of MMSE score and memory recall sub-score than the ADCI-DPP-4i^{-} group.

Abbreviation: ADCI = Alzheimer's disease-related cognitive impairment; DPP-4i = dipeptidyl peptidase-4 inhibitors; MMSE = Mini-Mental Status Examination.



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Association of Dipeptidyl Peptidase-4 Inhibitor Use and Amyloid Burden in Diabetic Patients With AD-Related Cognitive Impairment

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