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Association of Central Auditory Processing Dysfunction With Preclinical Alzheimer's Disease

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Abstract

Objective. To investigate whether central auditory processing dysfunction measured by the dichotic digit test-1 digit (DDT1) is present in preclinical Alzheimer's disease (AD) individuals who are cognitively normal (CN) older adults with the cerebral beta-amyloid (Aβ) deposition and to explore the potential of the DDT1 as a screening test for preclinical AD.

Study Design. Cross-sectional design.

Setting. A prospective observational cohort study.

Methods. CN older adults with a global clinical dementia rating score of 0 were included. The hearing test battery including pure-tone audiometry, speech audiometry, distortion product otoacoustic emission, and DDT1 was administered to participants.

Results. Fifty CN older adults were included. Among them, 38 individuals were included in the Aβ deposition negative (AN) group and 12 were included in the Aβ deposition positive (AP) group. The DDT1 scores of both the better and worse ears were significantly lower in the AP group than in the AN group ($p = .008$ and $p = .015$, respectively). No significant differences were observed between the groups in tests of the peripheral auditory pathways. In multivariable logistic regression analysis adjusted for apolipoprotein E4 positivity, the DDT1 better ear score predicted the AP group ($p = .036$, odds ratio = 0.892, 95% confidence interval: 0.780-0.985) with relatively high diagnostic accuracy.

Conclusion. Our findings suggest that Aβ deposition may affect the central auditory pathway even before cognitive decline appears. DDT1, which can easily be applied to the old-age population, may have the potential as a screening tool for preclinical AD.

Keywords

Alzheimer's disease, amyloid, central auditory processing dysfunction, dichotic digit test

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Alzheimer's disease (AD), which is currently the most common cause of dementia, is a neurodegenerative disease in which beta-amyloid (Aβ) deposition serves as a key neuropathological change. Because of the progressive and irreversible deterioration caused by AD, early detection of and intervention for the disease is tremendously important. Given that Aβ deposition begins decades before the onset of clinical symptoms,[1] the preclinical stage of AD, that is, the stage with Aβ deposition but no cognitive impairment, is the ideal target for the early detection of AD. Recently, the detection of preclinical AD has become more important because of the increased risk of clinical progression in the preclinical AD population.[2] As of now, both brain positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) examination of the Aβ biomarker are widely used for the early diagnosis of preclinical AD, with

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a high diagnostic accuracy in detecting AD neuropathological changes.[3-5] However, these methods have limitations in terms of cost, ease of availability, and invasiveness. Thus, there is still a need to develop a noninvasive and easy-to-implement test to detect or screen individuals in the preclinical stage of AD.

Numerous epidemiological studies have reported that hearing loss (HL) is one of the risk factors for AD dementia.[6-10] Moreover, although most previous epidemiological studies investigated peripheral HL, the presence of central auditory processing dysfunction (CAPD), which is another major contributor to HL in older adults,[11] was also found to be related to an increased risk of AD dementia.[12,13] Central auditory processing involves more complex tasks beyond simple sound detection to understand speech.[14] These tasks include auditory discrimination, sound localization and lateralization, and temporal processing. Individuals with CAPD have difficulties with speech comprehension due to problems with central auditory processing, even though there is no peripheral HL. Therefore, tests for central auditory processing can reflect brain changes that are independent of peripheral HL.[15] Previous studies have reported that performance on CAPD tests was associated with the score of neuropsychological tests after adjustment for peripheral HL in older adults.[16,17] In addition, the association between the CAPD test using the Dichotic Sentence Identification (DSI) test and CSF tau level was reported in nondemented individuals with a family history of AD-like dementia in a previous study.[18] However, whether CAPD is associated with preclinical AD remains unknown. If there is such an association, a test of central auditory processing may be used as a screening tool for preclinical AD.

Therefore, we aimed to investigate the association between CAPD and brain Aβ deposition in cognitively normal (CN) older adults. CAPD was measured using the dichotic digit test (DDT), which is a simple CAPD test that can be easily and quickly applied to older adults, including those with a low level of education or who are illiterate.[19] We additionally explored the potential of DDT as a screening test to detect preclinical AD.

Materials and Methods

Participants

Participants were recruited from an ongoing prospective cohort study, specifically the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE). Detailed information on the recruitment and inclusion/exclusion criteria for the KBASE study has been described previously.[20] For this study, CN older adults (55-90 years [inclusive]) who did not have mild cognitive impairment or dementia, with a global clinical dementia rating score of 0 were included. Participants with visual or HL to the extent that it interfered with neuropsychological examination were excluded. More precisely, subjects with HL that were considered moderately severe or worse in 1 or both ears were excluded (threshold mean > 55 dB HL at 0.5, 1, 2, and 3 kHz).[21,22] Participants with otolaryngology disorders that affected hearing, such as otitis media or aural atresia, were also excluded.

Comprehensive clinical and neuropsychological assessments based on the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) Assessment Packet,[23,24] multimodal neuroimaging, including [^{11}C] Pittsburgh imaging compound B (PiB)-PET and magnetic resonance imaging (MRI), and apolipoprotein E4 (APOE4) genotyping were administered to all participants. Regarding neuropsychological tests included in the CERAD-K neuropsychological assessment battery, tests for multiple cognitive domains, including global cognition, memory, language, visuospatial function, attention, and executive function, were administered to all participants (Supplemental Table S1, available online). The study was approved by the institutional review board of Seoul National University Hospital and written informed consent was obtained from all participants.

Examination of Peripheral and Central Auditory Function

Tympanic endoscopy and tympanometry (Madsen OTOflex 100 Handheld Tympanometer, Natus Hearing & Balance) were performed on all subjects, and only subjects with normal tympanic membrane findings were included in the study. Then, pure-tone audiometry (PTA), speech audiometry (SA), and distortion product otoacoustic emission (DPOAE) tests were performed as previously described.[25] All tests were performed in a sound-attenuating booth. Air conduction thresholds (dB HL) were measured at 0.25, 0.5, 1, 2, 3, 4, and 8 kHz using a Madsen Astera2 (Natus Hearing & Balance), and a threshold average at 0.5, 1, 2, and 3 kHz was calculated. Through SA, a speech reception threshold (dB HL) and speech discrimination score (%) were obtained. The 2f1-f2 DPOAE was measured with an ILO96 DPT OAE System (Otodynamics) with a frequency ratio (f2/f1) of 1.22.[25] The test results were presented as the results of the ear with the better DDT score and the ear with the worse DDT score.

For the CAPD tests, the dichotic digit test-1 digit (DDT1) was performed. The DDT1 is a test in which the subject answers with the numbers they heard; it can easily be performed regardless of the level of education. DDTs were delivered using an audiometer (Madsen OB922), a CD player, and earphones (Telephonics TDH 39). The delivered sound level was adjusted to the subject's comfort level and it was adjusted so that the subjective sound levels of both ears were the same. Monosyllabic digits (1, 3, 5, 6, 7, 8, 9, and 10) were presented in lists that contained a series of single digits. The list of single digits contained 20 pairs of digits that were delivered

simultaneously to both ears. The interstimulus interval was 4 or 5 seconds and the tests were carried out in a free-recall condition. In total, 20 trials were conducted. The number of times that the correct answer was spoken was calculated as a percentage for each ear. Among the scores for both ears, the higher score was called the better ear score, and the lower score was called the worse ear score.

Measurement of Cerebral Aβ Deposition

Simultaneous 3-dimensional (3D) [^{11}C] PiB-PET and a 3D T1-weighted MRI using a 3.0 T Biograph mMR (PET-magnetic resonance) scanner (Siemens) were obtained from all participants. The details of the image acquisition and preprocessing for the [^{11}C] PiB-PET and MRI were provided in our previous study.[26] Individuals were assigned to the amyloid-positive (AP) group if their standardized uptake value ratio (SUVR) was >1.4 in at least 1 of the 4 regions of interest (ROIs): the frontal, lateral parietal, posterior cingulate-precuneus, and lateral temporal regions; participants were assigned to the amyloid-negative (AN) group if their SUVR of all 4 ROIs was ≤1.4.[27-29]

Statistical Analysis

The comparison of demographic and clinical variables, as well as the performance of the peripheral auditory function test and the DDT1 score, was performed using a Mann-Whitney *U* test for continuous variables because of the non-normal distribution of data and the small sample size. The χ^2 or Fisher's exact test was used for the comparison of categorical variables. Next, we performed univariable logistic regression analyses for variables related to peripheral and central auditory function tests that showed significant differences between the 2 groups. Then, multivariable logistic regression analyses were performed including test-related variables that showed significance in the univariable logistic regression analyses step as independent variables. Age, sex, and APOE4 positivity were also included as independent variables in this multivariable logistic regression analysis. The dependent variable was set as amyloid positivity. The backward likelihood ratio (LR) method was used to select a model in the multivariable logistic regression analyses. Receiver operating characteristic (ROC) curve analysis was conducted to estimate the area under the curve (AUC) of the model. All statistical analyses except ROC curve analysis were done using IBM SPSS Statistics 26 and ROC analysis was done using MedCalc Software.

Results

A total of 52 subjects were recruited for this study. Among them, 1 subject of the AN group was excluded due to profound HL, and 1 subject of the AP group was excluded due to moderately severe HL. Finally, 38 and 12 subjects were included in the AN and AP groups, respectively.

The characteristics of the participants are described in **Table 1**. There was no significant difference between the AN and AP groups in terms of age, sex, or education level, and the APOE4 positivity rate was higher in the AP group ($p = .007$). With regard to the neuropsychological tests, there were no significant differences in tests for all cognitive domains between the 2 groups (Supplemental Table S1, available online).

When we compared the results of the DDT1 better ear score between the 2 groups using a Mann-Whitney *U* test (**Table 2** and **Figure 1**), the AP group showed lower performance than the AN group ($p = .008$). The DDT1 worse ear score of the AP group was also lower than that of the AN group ($p = .015$). In the univariable logistic regression analysis, both DDT1 better and worse ear scores showed significant associations with Aβ positivity in CN older adults ($p = .022$, odds ratio [OR] = 0.903, 95% confidence interval [CI]: 0.827-0.985 for the DDT1 better ear score; $p = .010$, OR = 0.933, 95% CI 0.885-0.984 for the DDT1 worse ear score). In contrast, no differences were found between the 2 groups regarding the results of the PTA, SA, and DPOAE tests (**Table 3**).

We performed a multivariable logistic regression analysis with Aβ positivity as a dependent variable and independent variables that included both the DDT1 better and worse scores, which showed significant

Table 1. Characteristics of Participants

	AN (N = 38)	AP (N = 12)	M-W *U* test *p* value
Age (y)	71 (63, 75)	74 (70, 80)	.082
Female	26 (68)	6 (50)	.246[a]
Education (y)	12 (9, 16)	12 (8, 16)	.963
APOE4 carriers	4 (11)	6 (50)	.007[b]
Global Aβ deposition (SUVR)	1.10 (1.06, 1.13)	1.63 (1.55, 1.96)	<.001

Data are presented as median (Q1, Q3) or N (%).

Abbreviations: AN, amyloid negative; AP, amyloid positive; APOE4, apolipoprotein E4; Aβ, beta-amyloid; M-W, Mann-Whitney; SUVR, standardized uptake value ratio.

[a]Pearson's χ^2 test.

[b]Fisher's exact test.

Table 2. Performance of Central Auditory Processing Tests in the AN and AP Groups

			M-W *U* test	Logistic regression	
	AN (N = 38)	AP (N = 12)	*p* value	*p* value	OR (95% CI)
DDT1 (%)					
Better ear	100.0 (95.0, 100.0)	95.0 (77.5, 100.0)	.008	.022	0.903 (0.827-0.985)
Worse ear	100.0 (90.0, 100.0)	85.0 (62.5, 98.8)	.015	.010	0.933 (0.885-0.984)

Data are presented as median (Q1, Q3).
Abbreviations: AN, amyloid negative; AP, amyloid positive; CI, confidence interval; DDT1, dichotic digit test-1 digit; M-W, Mann-Whitney; OR, odds ratio.

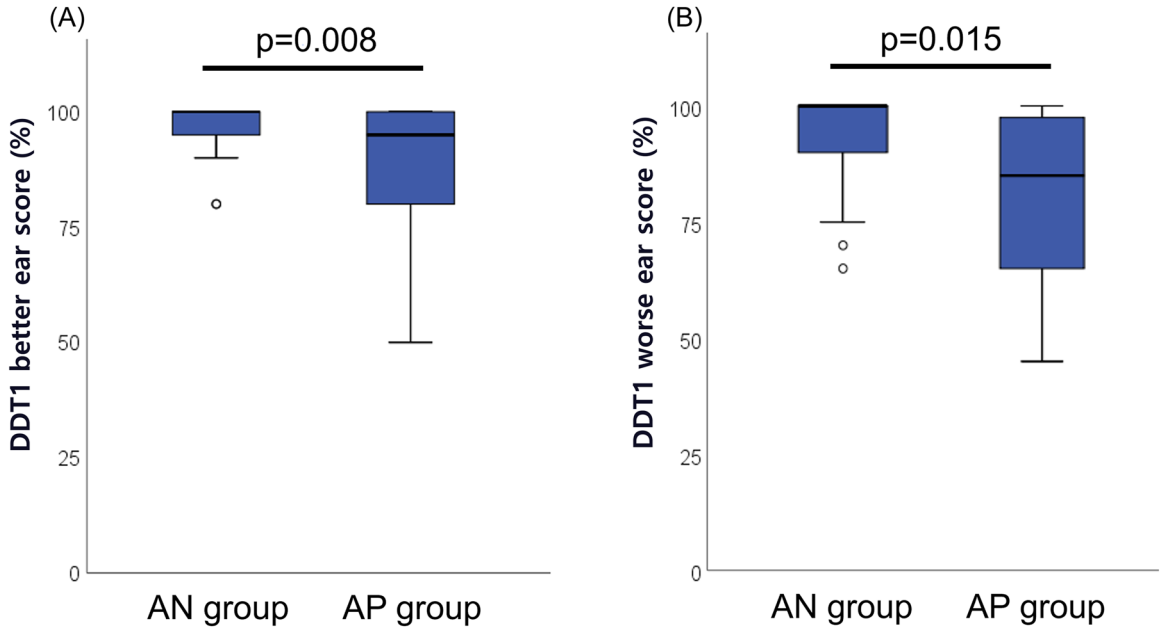

Figure 1. Performance of central auditory processing tests in the AN and AP groups. AN, amyloid negative; AP, amyloid positive; DDT1, dichotic digit test-1 digit.

differences between the 2 groups, and age, sex, and APOE4 positivity with the backward LR method for model selection. A model that included the DDT1 better ear score and APOE4 positivity as independent variables was selected ($p = .036$, OR = 0.892, 95% CI: 0.802-0.992 for the DDT1 better ear score; $p = .015$, OR = 8.363, 95% CI: 1.500-46.629 for APOE4 positivity). In a subsequent ROC curve analysis, the AUC of this model was 0.805 (95% CI: 0.668-0.903).

Discussion

In the present study, the AP group showed poorer performance on the DDT1 for both the better and worse ears than did the AN group, whereas there were no significant differences on the tests of the peripheral auditory pathways, including the PTA, SA, DPOAE, and the conventional neuropsychological tests based on CERAD-K neuropsychological battery. In addition, the AUC of the DDT1 better score for the discrimination of Aβ deposition in CN older adults was 0.805, which suggests that DDT1 could have potential as a screening test for preclinical AD.

Our findings are in line with previous studies that have reported deficits in dichotic listening tests in the clinically diagnosed AD dementia population,[30-32] as well as a study that revealed an association between DDT and an increased risk of AD dementia.[13] In addition, a recent systematic review reported that people with mild cognitive impairment showed worse results than healthy people on central auditory processing tests including DDT.[14] One previous study reported a relationship between the DSI test results and CSF tau levels, and not in CSF Aβ levels, in nondemented individuals with a family history of AD.[18] However, a direct comparison of this study with our study is difficult because of differences in the sample characteristics and methodologies between the 2 studies; the previous study investigated the relationship between the CSF biomarkers of AD but did not define the preclinical AD group using CSF biomarkers. In addition, the clinical sample characteristics were different from those of our study, as the previous study recruited individuals with a family history of AD rather than individuals from the general population. Differences between the CAPD tests (ie, the DSI vs the DDT1) might have also been involved in the differences.

Table 3. Performance of Peripheral Hearing Tests in the AN and AP Groups

	AN (N = 38)	AP (N = 12)	M-W *U* test *p* value
Pure-tone audiometry			
Air conduction threshold, average, dB HL			
Better ear	22.5 (17.5, 34.7)	21.9 (19.1, 34.4)	.785
Worse ear	21.3 (15.0, 29.1)	28.8 (16.6, 34.7)	.446
Speech audiometry			
Speech reception threshold, dB HL			
Better ear	20.0 (16.0, 32.5)	23.0 (18.5, 34.0)	.368
Worse ear	20.0 (14.0, 30.0)	25.0 (16.5, 34.0)	.322
Speech discrimination score (%)			
Better ear	92.0 (88.0, 96.0)	91.0 (85.0, 96.0)	.409
Worse ear	92.0 (90.0, 96.0)	91.0 (82.0, 96.0)	.267
DPOAE (dB SPL)			
SNR 1 kHz			
Better ear	3.8 (−5.3, 8.2)	−0.8 (−4.9, 4.4)	.261
Worse ear	2.2 (−1.8, 5.9)	−1.8 (−9.7, 6.9)	.340
SNR 1.4 kHz			
Better ear	9.8 (−1.7, 19.7)	5.0 (−0.7, 13.3)	.334
Worse ear	10.5 (3.4, 16.4)	6.6 (5.6, 14.8)	.540
SNR 2 kHz			
Better ear	8.6 (1.4, 15.5)	7.6 (2.4, 15.6)	.874
Worse ear	10.9 (3.2, 16.0)	8.5 (2.5, 13.6)	.586
SNR 2.8 kHz			
Better ear	−0.4 (−6.4, 10.6)	5.7 (−2.4, 10.7)	.525
Worse ear	4.6 (−3.8, 11.5)	5.7 (−1.5, 10.4)	.811
SNR 4 kHz			
Better ear	3.4 (−7.4, 9.0)	2.1 (−4.2, 9.4)	.683
Worse ear	1.7 (−5.2, 12.8)	7.3 (−5.3, 14.6)	.420
SNR 6 kHz			
Better ear	−0.4 (−6.5, 6.7)	−3.8 (−10, −1.5)	.220
Worse ear	−2.7 (−8.4, 8.0)	−5.8 (−15, 6.4)	.433

Data are presented as median (Q1, Q3).

Abbreviations: AN, amyloid negative; AP, amyloid positive; DPOAE, distortion product otoacoustic emission; HL, hearing loss; M-W, Mann-Whitney; SNR, signal-to-noise ratio; SPL, sound pressure level.

Considering that no significant differences were found between the AP and AN groups in terms of the neuropsychological tests included in the CERAD-K neuropsychological assessment battery, our finding suggests that the DDT1 better ear score can reflect AD-related neuropathological changes in the preclinical stage of AD more sensitively that do conventional neurocognitive tests. Dichotic listening involves the process of integrating or separating different sounds presented simultaneously to both ears, which requires abilities including executive functioning such as inhibition of irrelevant signals, as well as attention to task and short-term memory.[17,33,34] Considering previous reports supporting subtle changes in executive function before memory in cognitively unimpaired individuals with AD pathologies,[35,36] our findings might be partly related to neuropsychological characteristics of the dichotic listening test itself. In addition, conventional neuropsychological tests have complex neural correlates that involve multiple brain regions. In contrast, the dichotic listening test, particularly DDT1, is a very simple test that does not involve many neural pathways.[37] Thus, DDT1 might be more sensitive to detecting subtle cognitive deficits in the preclinical AD group, because the probability to be compensated by other mechanisms is much lower than that of conventional neuropsychological tests.

The mechanism by which Aβ deposition relates to impaired dichotic listening performance has not yet been clearly elucidated. However, it can be postulated that the effect of Aβ deposition on dichotic listening may be mediated by brain changes induced by Aβ accumulation based on previous studies.[38-43] The lateral temporal cortex which includes the auditory cortex is 1 of the brain regions that Aβ highly accumulates in AD.[39] Moreover, the auditory

pathway is composed of subcortical and corticocortical white matter (WM) tracts.[42] Altered WM microstructure is known to be associated with auditory processing disorders[41] and sensorineural HL.[43] According to previous studies, WM degeneration occurs even before the onset of symptoms in AD,[38] and early-stage amyloid pathology is associated with WM microstructure disruption.[40] Therefore, Aβ deposition in the preclinical stage of AD might be associated with damage to the pathway of dichotic listening, although further research will be necessary.

To develop a test that screens subjects at a preclinical stage of AD, 2 major considerations are required. First, the test should be simple and noninvasive and should be able to be performed at a low cost. Because the test will be performed on a large number of subjects without symptoms, if the test is difficult or expensive, it will be impossible to actually perform it. The second consideration is that the test should detect changes in the brain more sensitively than conventional neuropsychological tests so that changes in the brain that cannot be detected by conventional neuropsychological tests can be detected. Given this, the DDT1 is a good candidate. The dichotic listening test that uses numbers, like the DDT1, can be performed as long as the subject knows numbers, regardless of the level of education. It is relatively unaffected by peripheral HL[19,44] and shows high reliability in both young children and the elderly.[45,46] As such, the DDT1 can easily be conducted on elderly people. In terms of convenience and cost, the DDT1 is suitable as a screening test for the early diagnosis of AD in a wide range of old-age population adults without consideration for an educational level or peripheral HL.

This study used an analysis method that was different from those of previous studies that used the dichotic listening test. Several existing studies have analyzed dichotic listening test results by presenting the left and right ear scores. The dichotic listening test results generally show better results for the right ear in the free-recall condition, which is known as the right-ear advantage.[47,48] This is presumed to be because the crossed auditory pathways are more effective than the uncrossed auditory pathways, and the left hemisphere shows dominance for language processing.[48] However, it has been reported that the left ear showed better results or that there was no difference between the 2 sides in 15% to 22% of participants.[49-51] In our study, 18% of CN older adults (9 out of 50 participants) showed a left-ear advantage. The left-ear advantage is presumed to be due to mixed or reversed dominance of language.[52,53] We wanted to analyze the results according to dominance for language processing. The test results were presented according to DDT1 better and worse ear side rather than simply presenting them left and right.

There are some limitations to this study. First, as the sample size of the AP group was small, which may limit statistical power, further studies with a larger sample size will be needed. Second, the data for brain tau deposition, which is another hallmark of the neuropathology of AD, were not available in this study. Further studies that employ tau PET, as well as amyloid PET, will be helpful to understand in more detail the underlying mechanism between CAPD and AD. In addition, longitudinal follow-up studies will be helpful to further investigate the role of DDT1 as a screening tool for future cognitive decline in CN older adults with preclinical AD.

Conclusion

To the best of our knowledge, our study is the first to report deficits in DDT1 results in individuals with preclinical AD defined by an amyloid PET, which can detect in vivo cerebral Aβ deposition with relatively high accuracy. Based on these results, the DDT1 may reflect subtle cognitive changes associated with brain Aβ deposition in individuals at the preclinical stage of AD, that cannot be captured by conventional neuropsychological tests. Thus, DDT1, which is an easy and convenient test that can be applied to a wide range of older adults, may have the potential for use in screening preclinical AD.

Author Contributions

Min Soo Byun, concept and design, acquisition, analysis, or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, supervision; **Munyoung Chang**, concept and design, acquisition, analysis, or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding, supervision; **Dahyun Yi**, acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, administrative, technical, or material support; **Hyejin Ahn**, acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, administrative, technical, or material support; **Dongkyun Han**, acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, administrative, technical, or material support; **Seulki Jeon**, acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, administrative, technical, or material support; **Hyunsook Jang**, acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, administrative, technical, or material support; **Dong Young Lee**, concept and design, acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, obtained funding, supervision; **Seung Ha Oh**, concept and design, acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, supervision.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

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