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ORIGINAL ARTICLE

Attenuation of Choroidal Thickness in Patients With Alzheimer Disease

Evidence From an Italian Prospective Study

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Introduction: To compare the 12-month choroidal thickness (CT) change between Alzheimer disease (AD) patients and normal subjects.

Methods: In this prospective, observational study, 39 patients with a diagnosis of mild to moderate AD and 39 age-matched control subjects were included. All the subjects underwent neuropsychological (Mini Mental State Examination, Alzheimer disease Assessment Scale-Cognitive Subscale, and the Clinical Dementia Rating Scale) and ophthalmological evaluation, including spectral domain optical coherence tomography, at baseline and after 12 months. CT was measured manually using the caliper tool of the optical coherence tomography device.

Results: After 12 months, AD patients had a greater reduction of CT than controls ($P \leq 0.05$, adjusted for baseline CT, age, sex, axial length, and smoking).

Discussion: CT in patients with AD showed a rate of thinning greater than what could be expected during the natural course of aging.

Key Words: Alzheimer disease, biomarker, choroidal thickness, optical coherence tomography, enhanced depth imaging

(*Alzheimer Dis Assoc Disord* 2016;00:000–000)

Alzheimer disease (AD) is the most common cause of dementia in the elderlies. Progressive extracellular deposition of amyloid-β (Aβ) protein and the accumulation of fibrous material (neurofibrillary tangles) within some neurons represent the neuropathologic hallmarks of the disease.[1] These main pathologic features coexist with a number of structural and functional microvascular abnormalities identified in the brain of affected patients: cerebral blood flow reduction; loss or abnormal cholinergic innervation resulting in arterial hypercontractility and increased vascular resistance; vascular anatomical defects such as atrophy of arterioles and capillaries associated with reduced microvascular density and extensive endothelial degeneration; and cerebral amyloid angiopathy with Aβ deposits in the vascular smooth muscle cells of cerebral arterioles and around cerebral capillaries.[2–7] Altogether, these cerebral vascular changes are believed to decrease Aβ peptide clearance across the blood-brain barrier and to lead to oxidative stress and neurotoxicity that precede the onset of clinical dementia.[8–10]

Increasing evidence suggests that ocular vasculature may also be affected in AD and it has been speculated that ocular vascular changes share similar pathogenic mechanisms with that of cerebral vasculature. Retinal vascular abnormalities, such as vessels attenuation and reduction of retinal blood flow, have been described both in vivo, and in transgenic animal models of AD.[11–14]

More recently, choroidal involvement was also observed. In a previous study, our group, using high-resolution spectral domain optical coherence tomography (OCT), found a significant reduction of choroidal thickness (CT) in AD patients.[15] Bayan et al[16] confirmed this novel finding in a subsequent cross-sectional study on 31 AD patients. The similar thinning of the choroid was further demonstrated in a histopathologic study on a rat model of AD and human postmortem retinal samples from AD donors.[17] The choroid naturally thins with aging, with an estimated 1.56 μm decrease in thickness for each year of age.[18] Our working hypothesis is that CT in patients with AD may show a rate of thinning greater than what could be expected during the natural course of aging. Parallel with cerebral vascular impairment, choroidal thinning may represent a novel biomarker of disease severity and progression.

In this exploratory study we compared CT change over a period of 12 months between patients with AD and normal subjects.

METHODS

Study Subjects

This was a prospective, observational study on patients with a diagnosis of mild-to-moderate AD who were consecutively recruited at the outpatient clinic of the Department of Neurology and Psychiatry of the Umberto I University Hospital (Rome, Italy), from May 2012 to May 2014. Informed consent was obtained from all subjects involved in the study and the Local Ethics Committee approved the experimental protocol. The research followed the tenets of the Declaration of Helsinki.

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The diagnosis of probable AD was made according to the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer disease and Related Disorders Association (NINCDS-ADRDA) criteria.[19] The findings in some of these patients have previously been published in a precedent article.[15] Cognitively healthy, age-matched volunteers were enrolled, as controls, among the unaffected companions of patients attending the outpatients' service of the Eye Clinic of the Umberto I University Hospital. Patients and controls underwent physical and neurological assessment, standard laboratory tests, serum vitamin B_{12}, folate and thyroid hormone assays. A complete neuropsychological evaluation including the Mini Mental State Examination (MMSE), the Alzheimer disease Assessment Scale-Cognitive Subscale/11 items (ADAS-Cog), and the Clinical Dementia Rating Scale (CDR) was performed during the enrollment phase and was repeated at 12 months. Patients were included if they met the following criteria: age between 55 and 85 years; MMSE score between 19 and 26; CDR score between 1 and 2; a Modified Hachinski Ischemic Scale ≤ 4; have a magnetic resonance imaging scan showing cortical atrophy involving the medial temporal lobes and the hippocampus[20]; and have a Fazekas scales less than grade 2.[21] Patients' exclusion criteria were: secondary dementia (ie, vitamin deficiency or severe hypothyroidism, hydrocephalus, syphilis, alcohol abuse); degenerative dementia other than AD; or vascular dementia diagnosed according to the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.[22] Control subjects' cognitive inclusion criteria were: MMSE > 26, ADAS-Cog < 20, and CDR = 0. Patients and controls were excluded if they had: severe carotid artery stenosis; uncontrolled hypertension; diabetes mellitus; history of repeated head trauma or protracted loss of consciousness following head trauma within the last 5 years; severe central nervous system infections within the last 5 years; and history of cerebrovascular disease (ie, stroke, transient ischemic attacks, cerebral hemorrhage). We also excluded subjects suffering from psychiatric comorbidities or receiving antidepressant, antipsychotic or antiepileptic drugs. Anticholinesterase inhibitors were, instead, allowed.

Eye Examination

Patients and controls underwent a complete ophthalmologic evaluation, including best-corrected visual acuity (BCVA) measurements using the Early Treatment Diabetic Retinopathy Study chart at 4 m, ocular biometry (IOL Master, Carl Zeiss Meditec, Dublin, CA), anterior segment biomicroscopy, intraocular pressure with Goldmann tonometry, dilated fundus examination, fundus photography, and OCT.

Ocular exclusion criteria were: BCVA < 20/25; refractive error > ± 3 spherical equivalent; axial length < 22 and > 26 mm; intraocular pressure > 18 mm Hg, cup/disc ratio > 0.5; optic disc anomaly such as, tilted disc or peripapillary atrophy; pre-existing macular pathologies such as age-related macular degeneration (AMD), epiretinal membrane or macular hole; other retinopathies such as retinal vascular occlusion or retinal dystrophy; pre-existing ocular diseases such as glaucoma or uveitis; history of any neuro-ophthalmologic disease; amblyopia; previous intraocular surgery or laser treatment except for cataract surgery performed at least 12 months before enrollment; any intraocular surgery during the study period; use of topical medication or systemic therapy with known interference on retinal thickness such as steroids and diuretics; and low quality (< 20 units) OCT images.

In the included participants, the ophthalmologic evaluation, including BCVA measurement and OCT, was repeated after 12 months from baseline assessment as well as the neuropsychological assessment.

OCT

Patients and controls underwent OCT examination using the Heidelberg Spectralis (Spectralis Family Acquisition Module, Version 5.1.6.0; Heidelberg Engineering, Heidelberg, Germany) with Heidelberg Eye Explorer (Version 1.7.1.0), following a standardized protocol described elsewhere.[15] All scans were acquired in high-resolution mode by an experienced operator who was masked to the subject' diagnosis. Active eye tracking (TruTrack) and automatic follow-up scan (AutoRescan) were used to enable

TABLE 1. Alzheimer Disease Patients Versus Controls: Demographics and Baseline Clinical Characteristics

	AD Patients	Controls	*P*
Age (y)	71.1 ± 7.2	70.8 ± 6.7	0.8*
Sex (M/F)	18/21	17/22	1.0†
Memory symptoms duration (range, min to max) (y)	2.9 ± 1.7 1-7		
Axial length (mm)	23.5 ± 0.7	23.4 ± 0.6	0.5*
ACD (mm)	3.2 ± 0.5	3.2 ± 0.4	0.9*
Corneal curvature (mm)	7.8 ± 0.2	7.7 ± 0.3	0.9‡
Spherical equivalent (Diopters)	+ 0.6 ± 0.7	+ 0.5 ± 0.8	0.6‡
Phakic/pseudophakic	23/16	25/14	0.8†
Intraocular pressure (mm Hg)	13.8 ± 1.7	13.6 ± 1.4	0.6‡
BCVA (no. ETDRS letters)	54 ± 3.8	57 ± 4.1	$F = 7.4$ 0.009§
Scholar (range, min to max) (y)	9.0 ± 3.8 2-17	9.3 ± 4.7 5-17	0.8‡
MMSE score (range, min to max)	22.5 ± 2.1 19-26	28.6 ± 1.4 27-30	< 0.0001‡
ADAS-Cog (range, min to max)	31.1 ± 5.9 20-43	9.2 ± 3.5 3-19	< 0.0001‡
CDR (range, min to max)	1.4 ± 0.2 1-2	0.0 ± 0.0 0	< 0.0001‡
Glycaemia (mg/dL)	80.9 ± 6.7	81.6 ± 7.1	0.7*
LDL-cholesterol (mg/dL)	82.5 ± 11.4	81.3 ± 12.2	0.7*
Total-cholesterol (mg/dL)	197.3 ± 13.2	198.7 ± 13.0	0.6*
Systolic blood pressure (mm Hg)	132.7 ± 6.5	131.8 ± 7.0	0.6‡
Diastolic blood pressure (mm Hg)	74.7 ± 5.2	74.2 ± 5.9	0.7‡
Smoking/no smoking	11/28	9/30	0.8†

Values are mean ± SD unless otherwise indicated.
*Unpaired *t* test with Levene test for equality of variances.
†Fisher exact test.
‡Mann-Whitney *U* test
§Differences in BCVA between groups were determined by the general linear model including age, sex, and axial length as covariates.
ACD indicates anterior chamber depth; AD, Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale; BCVA, best-corrected visual acuity; CDR, Clinical Dementia Rating Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; MMSE, Mini Mental State Examination.

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TABLE 2. Alzheimer Disease Patients Versus Controls: Baseline Choroidal Thickness Measurements

	AD Patients	Controls	Coefficient, *P*	ICC (95% CI)*
Subfoveal CT (μm)	194.0 ± 70.8	284.3 ± 75.6	$F = 8.1$, 0.007†	0.98 (0.97-0.99)
Superior CT 500 (μm)‡	202.1 ± 74.8	277.9 ± 83.2	$F = 6.8$, 0.01†	0.97 (0.96-0.98)
Superior CT 1500 (μm)‡	210.8 ± 76.1	282.3 ± 81.8	$F = 6.8$, 0.01†	0.97 (0.96-0.98)
Inferior CT 500 (μm)‡	186.8 ± 76.0	268.5 ± 82.9	$F = 8.8$, 0.005†	0.96 (0.95-0.97)
Inferior CT 1500 (μm)‡	177.0 ± 74.8	270.9 ± 83.2	$F = 10.9$, 0.002†	0.97 (0.96-0.98)
Temporal CT 500 (μm)‡	200.4 ± 68.7	270.6 ± 71.4	$F = 6.2$, 0.02†	0.97 (0.96-0.98)
Temporal CT 1500 (μm)‡	194.9 ± 56.8	252.2 ± 60.0	$F = 5.8$, 0.02†	0.96 (0.94-0.98)
Nasal CT 500 (μm)‡	183.3 ± 79.3	267.8 ± 80.3	$F = 8.1$, 0.007†	0.97 (0.95-0.98)
Nasal CT 1500 (μm)‡	141.5 ± 67.5	204.8 ± 78.6	$F = 5.8$, 0.02†	0.96 (0.94-0.97)

Values are mean ± SD unless otherwise indicated.
*Interexaminer correlation coefficients for choroidal thickness measurements at baseline.
†Differences in measurements between groups were determined by the general linear model including age, sex, axial length, and smoking as covariates.
‡Denotes the position 500 μm superior to the fovea. The same naming convention is used for the subsequent entries.
AD indicates Alzheimer disease; CI, confidence interval; CT, choroidal thickness; ICC, intraclass test/retest correlation.

point-to-point correspondence between consecutive follow-up scans.

The spectral domain OCT images of the choroid were acquired by enhanced depth imaging modality. Two high quality, 30 degrees horizontal and vertical line scans through the fovea with 60 to 100 frames averaged for each scan were obtained. CT was measured using the manual caliper tool provided with the software of the OCT device. CT from the horizontal and vertical line scans was measured by 2 of the coauthors that were masked to the subjects' diagnosis, and values were averaged. These measurements were made of the subfoveal choroid and at 500 and 1500 μm from the center of the fovea.

Statistical Analysis

In prestudy sample size calculations, which were based on data from a previous study carried out in normal eyes,[36] enrollment of 38 eyes per group, would provide 80.0% power to detect as little as a 20% difference in the CT between cases and controls (assuming 2-sided tests and $\alpha = 0.05$). Sample size calculation was carried out with the commercial software IBM SPSS Sample Power for Windows (SPSS Inc., Chicago, IL). Statistical analysis was performed with the SPSS for windows (Version 17.0, SPSS). One eye from each participant was randomly chosen to perform the analysis. Normal distribution of data was analyzed by the Kolmogorov-Smirnov test. Parametric variables were compared using the unpaired *t* test. Levene test was used to verify variance homogeneity. Nonparametric distributed values were analyzed by the Mann-Whitney rank sum test. Categorical variables were compared using the Fisher exact test. Longitudinal data were analyzed using the paired *t* test or the Wilcoxon test, as appropriate. OCT measurements' changes from baseline between groups were compared using the general linear model, including the baseline OCT measurement, age, sex, axial length, and smoking as covariates. Bivariate relationships were evaluated by the Spearman coefficient or the Pearson analysis, as appropriate. Interobserver repeatability for CT measurements was tested with the intraclass test/retest correlation. Data are reported as mean values ± SD. *P*-values of < 0.05 were considered as statistically significant.

RESULTS

Baseline Evaluation

Altogether, 65 patients with AD were consecutively evaluated. Twenty patients were excluded at time of enrollment: 8 were affected with AMD, 5 had an epiretinal membrane, 3 were affected with glaucoma, 2 had high

TABLE 3. Alzheimer Disease Patients Versus Controls: Changes in Best-corrected Visual Acuity and Psychometric Scores Over 12 months

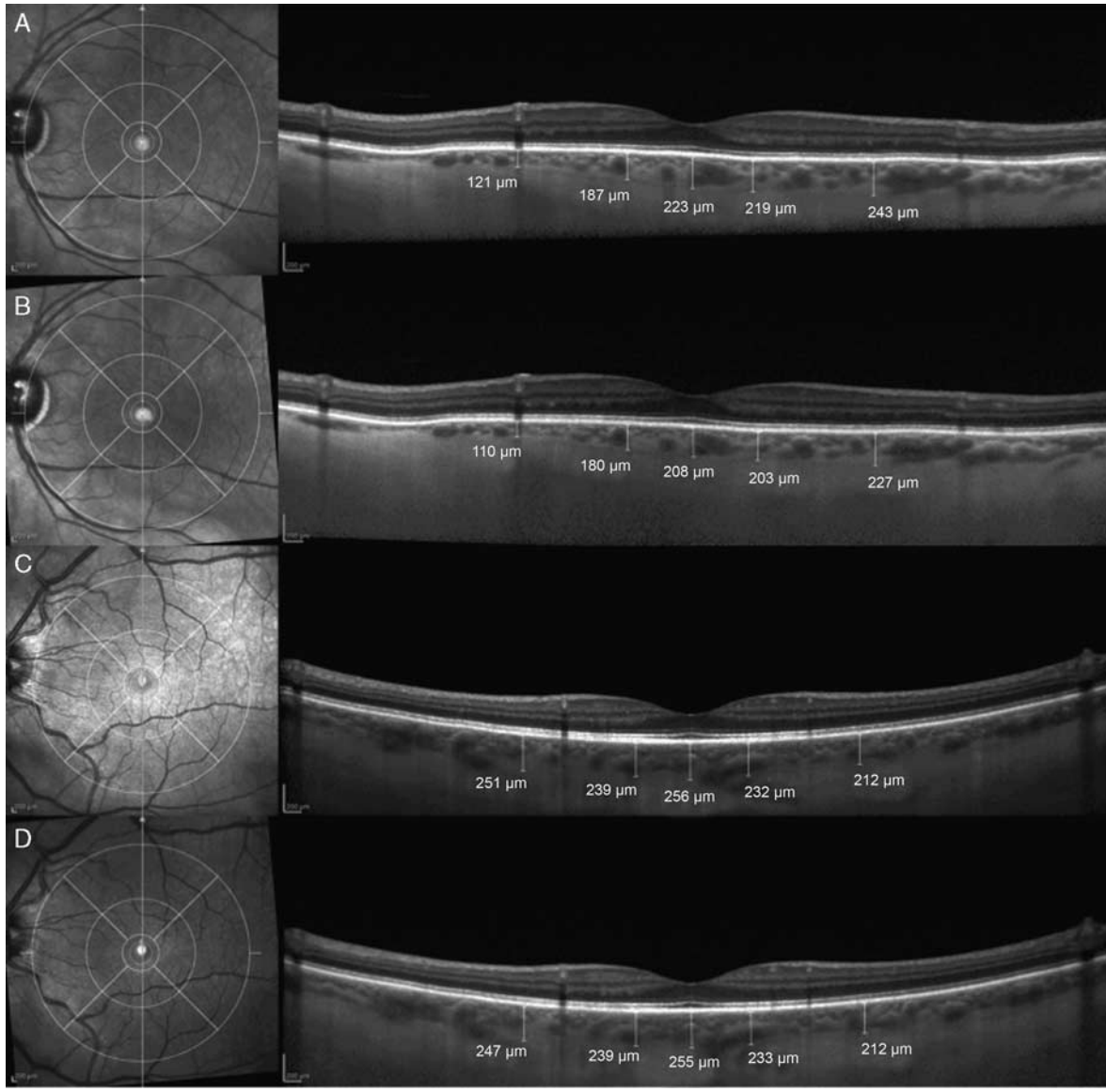
	AD Patients			Controls			
	T0	T12	*P*	T0	T12	*P*	*P*
BCVA (no. ETDRS letters)	54 ± 3.8	53 ± 3.5	0.01*	57 ± 4.1	57 ± 4.2	0.7*	
BCVA change	−1.3 ± 2.3			0.4 ± 2.1			$F = 9.6$, 0.004†
MMSE	22.5 ± 2.1	16.8 ± 2.8	< 0.0001‡	28.6 ± 1.4	28.3 ± 1.2	0.5‡	
MMSE change	−5.7 ± 4.0			−0.1 ± 1.1			< 0.0001§
ADAS-Cog	31.1 ± 5.9	38.7 ± 5.4	< 0.0001‡	9.2 ± 3.5	9.6 ± 3.1	0.3‡	
ADAS-Cog change	7.6 ± 4.3			−0.4 ± 1.3			< 0.0001§
CDR	1.4 ± 0.2	1.9 ± 0.3	< 0.0001‡	0.0 ± 0.0	0.0 ± 0.0	—	
CDR change	0.5 ± 0.4			0.0 ± 0.0			< 0.0001§

Values are mean ± SD unless otherwise indicated.
*Paired *t* test.
†Differences in BCVA change from baseline between groups were determined by the general linear model including baseline BCVA, age, sex, and axial length as covariates.
‡Wilcoxon test.
§Mann-Whitney *U* test.
AD indicates Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale; BCVA, best-corrected visual acuity; CDR, Clinical Dementia Rating Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; MMSE, Mini mental State Examination.

myopia, and 2 patients were excluded because of low quality OCT. Six patients dropped out during the 12-month follow-up period: 3 patients cited personal reasons and 3 underwent cataract surgery in both eyes. Thirty-nine eyes of 39 patients (mean age, 71.1 ± 7.2 y; range, 58 to 80 y; 21 women) with a diagnosis of mild to moderate AD and 39 eyes of 39 age-matched control subjects (mean age, 70.8 ± 6.7 y; range, 60 to 82 y; 22 women) were finally included in this 1-year prospective study. The demographic and clinical characteristics of patients at baseline are shown in Table 1. In AD patients, the Fazekas scores for periventricular and white matter hyperintensities were 0.70 ± 0.5 (range, 0 to 1) and 0.6 ± 0.5 (range, 0 to 1), respectively. Compared with controls, baseline BCVA was worse in AD patients ($F = 7.4$, $P = 0.009$). As expected, psychometric parameters (MMSE, ADAS-Cog, CDR) were all significantly worse in patients ($P < 0.0001$) compared with control subjects. At baseline, CT at each location was significantly reduced in AD compared with controls ($P < 0.05$, adjusted for age, sex, axial length, and smoking) (Table 2).

Month 12 Evaluation

After 12 months, the cognitive functions, as assessed by MMSE, ADAS-Cog 11, and CDR, were generally declined in patients ($P < 0.0001$) while remained unaffected in healthy subjects. Psychometric scores changes were all significantly different between groups ($P < 0.0001$). Compared with



AQ5 **FIGURE 1.** Representative images of choroidal thickness measurements as assessed with spectral domain optical coherence tomography in a patient with Alzheimer disease at baseline (A) and at month 12 (B). The patient's psychometric scores were: MMSE = 25, ADAS-Cog = 37, and CDR = 0.5, at baseline and MMSE = 20, ADAS-Cog = 41, and CDR = 1.5, at 12 months. Choroidal thickness measurements in a healthy subject at baseline (C) and at month 12 (D). Results of psychometric test were: MMSE = 29, ADAS-Cog = 8, and CDR = 0, at baseline and MMSE = 30, ADAS-Cog = 8, and CDR = 0, at 12 months. ADAS-Cog indicates Alzheimer disease Assessment Scale-Cognitive Subscale; CDR, Clinical Dementia Rating Scale; MMSE, Mini Mental State Examination.

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baseline, BCVA significantly decreased in patients ($P = 0.01$), while remained unchanged in controls. The BCVA decrease was significantly more prominent in AD patients compared with controls ($F = 9.6$, $P = 0.004$), (Table 3). Compared with baseline, CT at each location decreased significantly after 12 months in the AD group ($P < 0.001$) whereas no significant reduction was observed in controls (Fig. 1). The decrease in CT was significantly more prominent in patients compared with controls ($P \leq 0.05$, adjusted for baseline CT, age, sex, axial length, and smoking), (Table 4). No correlations were found between psychometric scores' changes and neither baseline CT nor CT changes.

DISCUSSION

Our results at 12 months showed a significant CT reduction in AD patients. Compared with healthy subjects, choroidal thinning was significantly more prominent in AD. It is noteworthy, that there is an age-related reduction in CT of about 1.6 μm for each year of age.[18] Herein, at 12 months, AD patients showed a mean decrease in subfoveal CT of about 10 μm, which is greater than what could be expected during the natural course of aging. This evidence suggests that the rate of choroidal thinning over time might represent a potential disease-specific event in AD, not linked to the physiological choroidal involution due to senescence.

In a precedent cross-sectional study, comparing CT between AD patients and healthy subjects, we demonstrated a significant reduction of CT in AD.[15] We postulated that choroidal thinning observed in AD might be related to a series of pathologic events triggered by local Aβ deposition similar to what can be found in the cerebral vascular system in AD.

Age-dependent Aβ accumulation in the choroidal vasculature has been demonstrated both in normal aging mouse and in a transgenic mouse model of AD.[23,24] More recently, Tsay et al demonstrated Aβ plaques accumulation in the AQ6 choroid as well as choroidal thinning in a novel transgenic rat model of AD.[17] In addition, the authors observed the recruitment of microglia and the activation of complement protein C suggesting an inflammatory response in the choroidal vascular system. As in the brain, Aβ accumulation in the choroid might induce inflammatory response and complement activation that progressively lead to neurodegeneration and vasoregression of the choroidal vasculature through the same pathologic cascade already described in AD brains.[4,25,26] Hence, the changes of CT we found in our patients could resemble, in vivo, the progression of the disease within the eye. Despite that, no significant correlation emerged between choroidal thinning and the psychometric scores. However, this could depend on the small size of the sample enrolled.

As highlighted in our previous article, the hypothesis that the reduction of CT in AD could depend on Aβ-mediated toxicity directly within the choroid is also in line with the evidences of similar mechanisms of choroidal damage in AMD, where Aβ accumulation has also been described.[27] Park et al[28] demonstrated that $A\beta_{42}$ was expressed in the retinal pigment epithelium layer of a mouse model of AD, which showed characteristic features of dry AMD. Of note, among the different phenotypes of AMD, the dry subtype is the one predominantly associated with choroidal thinning and atrophy. Further, it has recently been observed that patients with dry AMD are also at greater risk of cognitive impairment.[29] Hence, choroidal thinning found in our patients, similar to that described in AMD, further supports the hypothesis that a common pathogenic mechanism might exist between the 2 degenerative pathologies.

TABLE 4. Alzheimer Disease Patients Versus Controls: Measurements' Changes of Choroidal Thickness Over 12 months

	AD Patients			Controls				
	T0	T12	P	T0	T12	P	Coefficient, P	ICC (95% CI)*
Subfoveal CT (μm)	194.0 ± 70.8	183.3 ± 72.2	0.0001†	284.3 ± 75.6	282.4 ± 75.3	0.1†		0.98 (0.97-0.99)
Change	−10.7 ± 11.4			−2.0 ± 9.7			$F = 9.4$, 0.004‡	
Superior CT 500 (μm)§	202.1 ± 74.8	190.5 ± 74.2	0.0002†	277.9 ± 83.2	275.5 ± 80.2	0.3†		0.97 (0.95-0.98)
Change	−11.6 ± 11.9			−2.6 ± 10.8			$F = 4.4$, 0.04‡	
Superior CT 1500 (μm)§	210.8 ± 76.1	196.3 ± 72.1	< 0.0001†	282.3 ± 81.8	279.2 ± 81.3	0.1†		0.98 (0.97-0.99)
Change	−14.6 ± 14.4			−3.1 ± 10.0			$F = 5.2$, 0.03‡	
Inferior CT 500 (μm)§	186.8 ± 76.0	174.2 ± 75.2	< 0.0001†	268.5 ± 82.9	266.3 ± 80.4	0.1†		0.97 (0.95-0.98)
Change	−12.2 ± 11.5			−2.2 ± 10.7			$F = 6.0$, 0.02‡	
Inferior CT 1500 (μm)§	177.0 ± 74.8	164.8 ± 77.4	0.0005†	270.9 ± 83.2	266.7 ± 80.6	0.3†		0.96 (0.94-0.98)
Change	−12.2 ± 16.4			−4.1 ± 11.4			$F = 4.6$, 0.04‡	
Temporal CT 500 (μm)§	200.4 ± 68.7	189.7 ± 65.9	< 0.0001†	270.6 ± 71.4	267.4 ± 72.6	0.2†		0.96 (0.94-0.98)
Change	−10.8 ± 8.7			−3.2 ± 7.1			$F = 8.6$, 0.005‡	
Temporal CT 1500 (μm)§	194.9 ± 56.8	183.4 ± 55.2	0.0003†	252.2 ± 60.0	248.7 ± 59.1	0.1†		0.96 (0.94-0.98)
Change	−11.5 ± 13.1			−3.5 ± 8.9			$F = 7.4$, 0.01‡	
Nasal CT 500 (μm)§	183.3 ± 79.3	172.8 ± 77.5	< 0.0001†	267.8 ± 80.3	265.5 ± 79.5	0.3†		0.97 (0.95-0.98)
Change	−10.5 ± 8.6			−2.3 ± 7.9			$F = 6.3$ 0.02‡	
Nasal CT 1500 (μm)§	141.5 ± 67.5	128.9 ± 62.7	< 0.0001†	204.8 ± 78.6	202.4 ± 79.1	0.4†		0.97 (0.96-0.98)
Change	−12.6 ± 12.0			−2.4 ± 9.0			$F = 11.4$, 0.002‡	

Values are mean ± SD unless otherwise indicated.
*Interexaminer correlation coefficients for choroidal thickness measurements at 12 months.
†Paired *t* test.
‡Differences in measurements change from baseline between groups were determined by the general linear model including baseline choroidal thickness, age, sex, axial length, and smoking as covariates.
§Denotes the position 500 μm superior to the fovea. The same naming convention is used for the subsequent entries.
AD indicates Alzheimer disease; CI, confidence interval; CT, choroidal thickness; ICC, intraclass test/retest correlation.

Our finding that AD patients had significantly poorer visual acuity when compared with their normal counterpart should be emphasized. Accordingly, compared with controls, AD patients showed a significant visual acuity worsening over time. Our results are consistent with those of a recently published study by Nolan et al.[30] The visual dysfunction in AD has previously been thought to be only attributed to damage in the primary visual cortex and higher cortical areas. However, increasing evidence shows that precortical degeneration also plays a role.[31–33] Given its important role in maintaining retinal pigment epithelium and outer retina, the choroid is considered to be important for visual acuity.[34] Indeed, a direct correlation between CT and visual acuity has recently been shown in major ocular pathologies such as myopia and AMD.[35–37]

The main limitations of the present study are the small sample size and that choroidal analysis was based on nonautomated measurements on 2 single-line OCT scans. Further, as we did not use cerebrospinal fluid biomarkers or scans with Aβ PET ligands, some issues on diagnostic accuracy in our sample could arise. The strengths of this work include the prospective, longitudinal design, and the high rate of adherence to a strict protocol.

In conclusion, our study demonstrated that, compared with healthy subjects, AD patients showed a significant greater reduction of CT over a period of 12 months. However, future studies using the state-of-the-art instruments (ie, swept source OCT) are necessary to confirm our observations. Further appropriate prospective comparative studies of larger patient populations are also needed to establish the diagnostic and prognostic role of OCT analysis compared with the other dynamic research biomarkers available in AD.

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