Posterior pole analysis and ganglion cell layer measurements in Alzheimer’s disease

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ABSTRACT

**Aim:** To compare posterior pole analysis and ganglion cell layer (GCL) of patients with Alzheimer’s disease (AD) and controls.

**Method:** Patients diagnosed with mild and moderate AD included in the study. Posterior pole analysis and GCL measurements were investigated by dividing the macula into superior and inferior hemifields and 5 corresponding zones.

**Results:** There were no significant differences between groups for retinal thickness measurements in any retinal zone. GCL measurements showed lower measurements in moderate AD group for GCL thickness in the superior zone 2 (p=0.025) and inferior zone 2 (p = 0.048) compared to mild AD and controls. A moderate AD status was found to cause a decrease of 5.349 µm in the GCL-SZ2 value (p=0.037).

**Conclusion:** GCL measurements in the moderate AD group show significant thinning in superior and inferior Zone 2, which may be a biomarker for AD.

Introduction

Alzheimer’s disease (AD) is a common neurodegenerative disease of the elderly and the leading cause of dementia [1]. It is characterized by progressive loss of cognitive ability and impairs the daily activities of a person [2]. The disease leads to great consequences not only for the patients but also for their relatives from medical, emotional, and economical aspects.

Population-based studies show the incidence of dementia including AD is increasing. By the year 2030, it is expected that 65.7 million people will live with dementia [1].

Pathologic AD starts a decade earlier than clinical dementia, involving accumulation of intracellular neurofibrillary tangles of hyperphosphorylated tau protein (p-Tau) and extracellular beta-amyloid (Aβ) protein deposits throughout the brain [3,4]. Current diagnostic tools to detect AD at this stage are both invasive and expensive including magnetic resonance imaging (MRI), positron emission tomography, or cerebrospinal fluid analysis.

Recent clinical studies found that in addition to the atrophy of parietal cortex and primary visual cortex, anterior visual pathway degeneration may also play a role in AD pathogenesis [5,6]. This led many investigators to concentrate on whether any diagnostic tool can be found to detect AD earlier. After first histologic evidence of optic neuropathy and retinal ganglion cell degeneration in patients with AD, postmortem studies showed preferential superior and inferior temporal foveolar retinal ganglion cell degeneration [7]. In vivo studies also supported these findings by showing optic neuropathy, retinal nerve fiber layer degeneration, and macular thickness and volume losses [8,9].

In this current study, the macular ganglion cell layer and posterior pole analysis were analyzed for any superior-inferior asymmetry or localized GCL or retinal thickness loss in AD, different from healthy controls.

Methods

This was a cross-sectional study investigating the retinal OCT changes of patients diagnosed with AD. This study was approved by the local ethical committee with the registration number of HNEAH-KAEK and informed consent was obtained from the patients or relatives of the patients. This study adhered to the tenets of the Declaration of Helsinki. Between February 2020 to June 2020, patients diagnosed with AD at the neurology department were referred to the ophthalmology clinic and underwent detailed ophthalmologic examination including visual acuity measured by Snellen chart converted to logarithm of minimal angle resolution (LogMar), refraction noted as spherical equivalent (SE), intraocular pressure (IOP) measurement with the applanation tonometry, anterior segment, and dilated posterior segment examination. OCT scans were performed in the same session as the glaucoma protocol for RNFL analysis and posterior pole mode to analyze the 8*8 grid for retinal thickness (RT) and GCL analysis.

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Study subjects
Alzheimer’s disease diagnosis was made by a specialist neurologist based on the National Institute on Aging—Alzheimer’s Association (NIA-AA) criteria [10]. All patients had MRI and blood tests to exclude other etiologies for dementia. Patients diagnosed as dementia with probable AD were grouped as mild AD if mini-mental state examination test (MMSE) points >19 and as moderate AD if MMSE points ≤19. The control group included patients referred by a neurologist with minimal memory complaints with no AD and any other neurological disorder with MMSE function above 24 or normal healthy patients attending the ophthalmology clinic without any memory complaint and any neurological disorder. MMSE was applied to all AD and control patients referred from the neurology department by a clinical psychologist.

Inclusion criteria
All patients had probable AD diagnosis made by a specialist neurologist with MMSE points below 24. No neurologic diseases other than AD were present. On ophthalmologic examination, refractive errors were within the +/-4 D spherical error, <3 D cylindrical error, IOP <21 mmHg without any antiglaucomatous drug use, no retinal and optic nerve pathology, and no intraocular surgery history other than uncomplicated cataract surgery 1 year before. OCT scans with good image quality were included in the analysis.

Exclusion criteria
Patients with any neurologic disease other than AD, refractive error more than ± 4 D spherical and 3 D cylindrical errors, IOP above 21 mmHg or antiglaucomatous drugs usage, any retinal or optic nerve diseases, intraocular surgery history at any time other than cataract surgery or cataract surgery within the last 1 year, and media opacities precluding high-quality retinal imaging were not included into the study.

Controls
Patients referred from the neurology clinic with MMSE score above 24, no clinical dementia, and normal MRI findings ruling out AD diagnosis were included in the control group. Patients attending the ophthalmology clinic without any memory complaints and neurological diseases in their medical records and aged above 60 were included in the control group. Ophthalmologic inclusion and exclusion criteria were the same as for the study group, as mentioned above.

OCT images
In this study, ultra-high-resolution, SD-OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) was used for OCT scans. All scans were taken in the same session. Glaucoma protocol for posterior pole mode and high-speed mode of retinal nerve fiber layer (RNFL) scans were used. One grand mean and 6 quadrants including superotemporal (ST), superonasal (SN), nasal (N), inferonasal (IN), inferotemporal (IT), and temporal (T) values were analyzed for peripapillary RNFL measurements. For posterior pole scans, ‘8x8 Posterior Pole Grid’ was available. The right symmetric fovea-to-disc alignment of all scans was ensured. The ‘retina thickness’ graph displayed on the cSLO image showed the retinal thickness over the entire posterior pole 30°x25° OCT volume scan in 64 cells. We divide 64 cells into the 5 corresponding superior and inferior zones as described in Um et al.’s study [11] where zone 1 is closest to the fovea while Zone 4 and 5 are nearest the temporal and nasal side of the vascular arcades, respectively (Figure 1a). Scans with low image quality or any image discontinuity seen in cSLO images were not included in the analysis.

Posterior pole analysis
Posterior pole scans measured the macular thickness from the retina pigment epithelium (RPE)-Bruch membrane complex to
internal limiting membrane (ILM) individually on an 8°8 posterior pole grid. Automatic calculation tools gave a total grand mean macular thickness, superior and inferior mean thickness. Additionally, posterior pole scan were used in this study similar to that by Um et al. [11] to analyze retinal thickness in 5 corresponding macular zones (Figure 1a). Differences between the groups for the superior/inferior asymmetry of the corresponding zonal thicknesses were examined by extracting inferior mean zonal thickness from the corresponding superior values.

**Ganglion cell layer measurements**

For posterior pole scans, SPECTRALIS segments the ganglion cell layer independent of the inner plexiform and retinal nerve fiber layers so that detection of any loss from each anatomic component of the retinal ganglion cells is possible. GCL analysis was made by automatic segmentation in 64 macular cells. Total, superior and inferior GCL thickness were analyzed. GCL analysis in 5 corresponding macular zones (Figure 1b) and superior/inferior asymmetry between the corresponding zones for each group were analyzed as explained previously.

GCL total RT ratio was calculated separately for 5 zones to identify any differential GCL loss in the AD groups.

**Statistical analysis**

Number Cruncher Statistical System (NCSS) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used when evaluating the study data. Since quantitative data were included in the study with bilateral eyes in group comparisons, they were taken as dependent and evaluated with generalized linear mixed models (GLMM). The Independent Samples t-Test was used for group comparisons of normally distributed data. Pearson Chi-Square test was used to compare qualitative data. As multivariate analysis, GLM was used to determine the correlation levels between parameters. All parameters are evaluated in the model when the p-value <0.2. Significance was evaluated at the p < 0.05 level.

**Results**

A total of 38 patients with AD diagnosis referred to the ophthalmology clinic were evaluated. Among them, 23 met the inclusion criteria and were included in the study for statistical analysis; 13 were included in the mild AD group and 10 in the moderate Alzheimer disease group according to their MMSE scale results. The control group included 32 patients. Overall, the study was conducted with 100 eye measurements of 55 cases, 32.7% (n = 18) male and 67.3% (n = 37) female. Unilateral eyes of 18.2% (n = 10) and bilateral eyes of 81.8% (n = 45) of the cases were included in the study. In the study, the right eye of 47.0% (n = 47) and the left eye of 53.0% (n = 53) of the cases were evaluated. The ages of the cases ranged from 54 to 90, with a mean of 72.0 ± 7.92 years.

In total, 22 eyes of 13 patients in the mild AD group, 16 eyes of 10 patients in the moderate AD group, and 62 eyes of 32 patients in the control group were included in statistical analysis.

The mean age of the mild AD group was 77.00 ± 6.15 (65–85) years, the mean age of the moderate AD group was 73.9 ± 11.5 (54–90) and the mean age of the control group was 69.4 ± 6.1 (61–82) years. A statistically significant difference was found between the ages of the cases according to the groups (One-Way ANOVA, p = 0.008). The mean age of the mild AD group was higher than that of the control group.

In terms of sex, 4 (30.8%) of the mild AD, 3 (30%) of the moderate AD, and 11 (34.4) of the control cases were male. No statistically significant difference was found between the gender distribution of the cases according to the groups (Fisher-Freeman-Halton exact test, p > 0.05).

The mean MMSE score was 21.4 ± 1.3 for the mild AD group and 16.2 ± 1.3 for the moderate AD group (Independent Samples test, p < 0.001).

No statistically significant difference was found between the LogMar and SE values of the groups (p > 0.05). No statistically significant difference was found in terms of lens status of the cases among the groups (p > 0.05).

A statistically significant difference was found between the groups in terms of IOP values (p = 0.006). The values in the moderate AD group were found to be lower than those of the mild AD and control groups (p = 0.013, p = 0.002, respectively).

When the measurements are compared with GLM, superior mean retinal thickness (RT), grand mean RT, and inferior mean RT measurements of the cases did not show statistically significant differences according to the groups (p > 0.05). (Table 2) Retinal thickness of superior zone (RT-SZ)1, RT-SZ2, RT-SZ3, RT-SZ4, and RT-SZ5 measurements and corresponding (retinal thickness of inferior zone)RT-IZ1, RT-IZ2, RT-IZ3, RT-IZ4 and RT-IZ5 measurements of the cases did not have statistically significant differences between the groups (p > 0.05). RT-D1, RT-D2, RT-D3, RT-D4 and RT-D5, which were calculated by extraction of mean inferior zonal retinal thickness values from the controlling superior mean zonal measurements, of the cases did not have statistically significant differences between the groups (p > 0.05).
Table 1. Evaluation of Descriptive Characteristics by Groups.

|                          | Mild AD (n = 22) | Mod AD (n = 16) | Control (n = 62) | P     |
|--------------------------|------------------|-----------------|------------------|-------|
|                          | Mean ± Sd        | Mean ± Sd       | Mean ± Sd        |       |
| Logmar                   | 0.25 ± 0.18      | 0.12 ± 0.18     | 0.11 ± 0.17      | 0.052 |
| Spherical equivalent (diopter) | 0.14 ± 1.5      | 0.61 ± 1.5      | 1.17 ± 1.5       | 0.108 |
| IOP (mmHg)               | 15.51 ± 2.4      | 12.94 ± 2.4     | 15.77 ± 2.35     | 0.006*|
| Phasic n(%)              | 17 (77.3)        | 13 (81.3)       | 56 (90.3)        | 0.346 |
| Pseudophasic n(%)        | 5 (22.7)         | 3 (18.8)        | 6 (9.7)          |       |

*GLMM (Generalized Linear Mixed Model)
*p < 0.05

Table 2. Evaluation of RT and GCL Measurements by Group.

|          | Mild AD (n = 22) | Mod AD (n = 16) | Control (n = 62) | P  |
|----------|------------------|-----------------|------------------|----|
|          | Mean ± Sd        | Mean ± Sd       | Mean ± Sd        |    |
| RT Superior S | 280.24 ± 12.36  | 281.14 ± 12.41  | 280.26 ± 12.47   | 0.369|
| RT Total   | 280.26 ± 12.47   | 280.26 ± 12.02  | 286.09 ± 12.25   | 0.289|
| RT Inferior| 280.12 ± 12.95   | 279.26 ± 13.02  | 286.83 ± 12.77   | 0.217|
| RT-Z1     | 305.57 ± 23.21   | 303.09 ± 23.43  | 314.09 ± 22.65   | 0.308|
| RT-Z2     | 311.31 ± 17.61   | 309.91 ± 17.74  | 321.63 ± 17.28   | 0.078|
| RT-Z3     | 279.09 ± 13.65   | 277.61 ± 13.8   | 282.7 ± 13.26    | 0.503|
| RT-Z4     | 264.16 ± 11.44   | 267.06 ± 11.53  | 268.4 ± 11.21    | 0.527|
| RT-Z5     | 281.13 ± 13.54   | 283.31 ± 13.67  | 287.11 ± 13.23   | 0.363|
| RT-Z1     | 309.14 ± 23.95   | 307.56 ± 24.13  | 320.2 ± 23.49    | 0.211|
| RT-Z2     | 308.72 ± 17.58   | 304.75 ± 17.7   | 317.87 ± 17.27   | 0.070|
| RT-Z3     | 282.3 ± 14.18    | 278.85 ± 14.41  | 285.89 ± 13.63   | 0.358|
| RT-Z4     | 260.51 ± 13.35   | 258.81 ± 13.45  | 265.49 ± 13.1    | 0.281|
| RT-Z5     | 286.93 ± 18.81   | 283.3 ± 18.87   | 293.01 ± 18.65   | 0.300|
| RT-Δ1     | –3.5 ± 10.21     | –4.85 ± 10.4    | –5.99 ± 9.73     | 0.747|
| RT-Δ2     | 2.66 ± 8.03      | 4.61 ± 8.13     | 3.78 ± 7.78      | 0.842|
| RT-Δ3     | –3.03 ± 5.6      | –1.55 ± 5.74    | –3.25 ± 5.26     | 0.707|
| RT-Δ4     | 4.07 ± 9.46      | 7.27 ± 9.63     | 2.96 ± 9.05      | 0.458|
| RT-Δ5     | –5.38 ± 12.74    | –0.87 ± 12.92   | –5.76 ± 12.29    | 0.566|
| GCL Superior S | 30.6 ± 3.51     | 30.43 ± 3.54    | 31.36 ± 3.45     | 0.679|
| GCL Total   | 30.32 ± 3.91     | 30.01 ± 3.93    | 32.05 ± 3.85     | 0.215|
| GCL Inferior| 30.09 ± 4.7      | 29.67 ± 4.73    | 32.75 ± 4.62     | 0.087|
| GCL-Z1     | 37.94 ± 8.62     | 31.62 ± 8.66    | 36.91 ± 8.52     | 0.175|
| GCL-Z2     | 41.26 ± 6.95     | 35.73 ± 6.97    | 42.71 ± 6.9      | 0.025*|
| GCL-Z3     | 34.35 ± 6.37     | 30.21 ± 6.4     | 32.56 ± 6.3      | 0.309|
| GCL-Z4     | 28.78 ± 3.4      | 29.22 ± 3.44    | 28.99 ± 3.3      | 0.955|
| GCL-Z5     | 25.19 ± 9        | 29.56 ± 9.03    | 29.18 ± 8.93     | 0.361|
| GCL-Z1     | 38.94 ± 9.27     | 34.41 ± 9.31    | 39.59 ± 9.18     | 0.302|
| GCL-Z2     | 39.87 ± 6.36     | 36.51 ± 6.62    | 42.16 ± 6.2      | 0.049*|
| GCL-Z3     | 36.38 ± 6.61     | 32.68 ± 6.65    | 36.03 ± 6.62     | 0.330|
| GCL-Z4     | 26.35 ± 5.11     | 26.32 ± 5.16    | 28.81 ± 5        | 0.211|
| GCL-Z5     | 23.71 ± 13.35    | 26.39 ± 13.51   | 29.85 ± 13.46    | 0.364|
| GCL-Δ1     | –0.86 ± 4.92     | –2.92 ± 5.02    | –7.28 ± 4.68     | 0.456|
| GCL-Δ2     | 1.59 ± 4.02      | –0.77 ± 4.11    | 0.6 ± 3.81       | 0.390|
| GCL-Δ3     | –2.05 ± 2.49     | –2.74 ± 2.55    | –3.48 ± 2.34     | 0.194|
| GCL-Δ4     | 2.44 ± 4.9       | 2.76 ± 4.97     | 0.18 ± 4.75      | 0.200|
| GCL-Δ5     | 1.55 ± 6.44      | 2.92 ± 6.5      | –0.69 ± 6.3      | 0.244|

GLMM (Generalized Linear Mixed Model)

When the measurements are compared with GLMM among the groups, the superior mean GCL, grand mean GCL and inferior mean GCL measurements of the cases did not show statistically significant differences (p > 0.05). (Table 2) Ganglion cell layer of superior zone (GCL-Z1), GCL-Z3, GCL-Z4, and GCL-Z5 measurements of the cases and corresponding Ganglion cell layer of inferior zone (GCL-I21, GCL-I23, GCL-I24, and GCL-I25) measurements did not have statistically significant differences between the groups (p > 0.05). GCL-Δ1, GCL-Δ2, GCL-Δ3, GCL-Δ4 and GCL-Δ5 measurements of the cases did not show statistically significant differences according to the groups (p > 0.05).

A statistically significant difference was found for the GCL-Z2 measurements of the cases between the groups (p = 0.025; p < 0.05). The values in the moderate AD group were lower than that of the control group (p = 0.007). There was a statistically significant difference between the GCL-I22 measurements of the cases according to the groups (p = 0.048; p < 0.05). The values of the moderate AD group were lower than the control group (p = 0.030).

When GCL/RT ratios are compared among the groups, a statistically significant difference was found between the GCL/RT-Z2 ratio of the cases according to the groups (p = 0.018; p < 0.05). (Table 3) The values of the
Table 3. Evaluation of GCL/RT Ratios by Groups.

|          | Mild AD (n = 22) | Mod AD (n = 16) | Control (n = 62) | Mean ± SD | Mean ± SD | Mean ± SD | p     |
|----------|-----------------|-----------------|-------------------|----------|----------|----------|-------|
| GCL/ RT  |                 |                 |                   |          |          |          |       |
| Superior | 0.109 ± 0.011   | 0.108 ± 0.011   | 0.11 ± 0.01      | 0.883    |          |          |       |
| GCL/ RT Total | 0.108 ± 0.012 | 0.107 ± 0.012 | 0.112 ± 0.012 | 0.377    |          |          |       |
| GCL/ RT Inferior | 0.107 ± 0.015 | 0.106 ± 0.015 | 0.114 ± 0.015 | 0.161    |          |          |       |
| GCL/ RT -I2Z | 0.129 ± 0.017  | 0.118 ± 0.017   | 0.126 ± 0.021   | 0.352    |          |          |       |
| GCL/ RT -I3Z | 0.129 ± 0.021  | 0.116 ± 0.021   | 0.126 ± 0.021   | 0.352    |          |          |       |
| GCL/ RT -I2Z | 0.101 ± 0.017  | 0.101 ± 0.017   | 0.108 ± 0.017   | 0.319    |          |          |       |
| GCL/ RT -I2Z | 0.083 ± 0.047  | 0.094 ± 0.047   | 0.102 ± 0.045   | 0.444    |          |          |       |

GLMM (Generalized Linear Mixed Model)

moderate AD group were found to be lower than those of the mild AD and control groups (p = 0.019, p = 0.006, respectively).

Mean peripapillary RNFL thickness was 99.4 ± 12.0 μm, 100.1 ± 12.1 μm, and 97.8 ± 11.7 μm in the mild AD, moderate AD, and control groups, respectively. Mean RNFL measurements and superotemporal, nasal, inferonasal inferotemporal, and temporal quadrant measurements of the cases did not show statistically significant differences between the groups (p > 0.05). (Figure 2)

A significant difference was found for the superonasal RNFL measurements between the groups (p = 0.044; p < 0.05). RNFL measurements in the superonasal quadrant were higher in the moderate AD group than the control group (p = 0.030).

A model was created using GLMM to analyze variables affecting GCL-SZ2 and IZ-2 and it included only variables of p value<0.2. The model including age, groups, LogMar, IOP, and SE measurements as independent variables, which affected the GCL-SZ2 measurement, was found to be statistically significant (F(3,476); p=0.004). (Table 4) The effects of age and group variables in the model were found to be statistically significant (p<0.003; p<0.033, respectively). A1-year increase in age caused a 0.392 μm decrease in GCL-SZ2 value [Beta (95% CI) = −0.392 (−0.643, −0.142), p = 0.003]. Moderate AD status was found to cause a decrease of 5.349 μm in the GCL-SZ2 value [Beta (95% CI) = −5.349 (−10.358, −0.341), p = 0.037].

Similarly, the model in which age, groups, Logmar, IOP, and SE measurements, which were thought to affect the GCL-I2Z measurement, were included as independent variables, was found to be statistically significant (F(2.679; p=0.019). The effect of the age variable in the model was statistically significant (p=0.011). A 1 year increase in age caused a 0.320 μm decrease in GCL-I2Z value [Beta (95% CI) = −0.320 (−0.565, −0.075), p = 0.011].

A similar model was created for GCL/RT-SZ2 measurements and it was found to be statistically significant (F(3.376; p=0.005). The effects of age and group variables in the model were statistically significant (p<0.003; p<0.017, respectively). It was determined that a 1 year increase in age caused a 0.101 unit decrease in GCL/RT-SZ2 ratio [Beta (95% CI) = −0.101 (−0.202, −0.001), p = 0.003]. Moderate AD status was found to cause a 0.105 unit decrease in GCL/RT-SZ2 [Beta (95% CI) = −0.105 (−0.208, −0.001), p = 0.035].

Discussion

AD is a progressive neurodegenerative disorder that leads to the most common form of dementia. In addition to neurocognitive symptoms, patients with AD suffer from visual symptoms including impairments of visual acuity [12], contrast sensitivity [13], color perception [14], visual field [15], and motion perception [16]. These symptoms are not purely due to parietal and primary visual cortex involvement. There is increasing evidence about the role of anterior visual pathway degeneration in AD pathogenesis [17]. Many in vivo OCT studies showed optic nerve and retinal changes in patients with AD [8]. Histologic studies showed ganglion cell loss in AD and this loss was found to be different from normal aging, in which GCL loss was found to be mostly peripheral whereas GCL loss was macular in AD [5]. In AD, thinning of GCL was found to occur temporally in some studies and superior and inferior regional losses were reported in the others [5,7].

There are two hypotheses about the GCL loss in AD. The first proposed that the primary cerebral pathologic process may affect the visual pathway and lead to retrograde degeneration of the optic nerve and subsequently GCL loss [6]. This hypothesis is supported by evidence about the involvement of lateral geniculate nucleus and superior colliculus in AD. The second hypothesis proposed the simultaneous involvement of the brain and retina in the primary pathology, which is supported by the identification of characteristic Aβ plaques in ocular tissues [18].

Swept-source and Fourier domain OCT technology provides very high-resolution retinal images up to 3 μm axial resolution. This assists in investigating retinal layers individually in many disease processes. From the perspective of AD and ocular relationships, OCT provides very useful information. While RT and GCL measurements reflect the neuronal loss in GCL, RNFL thickness measurements give information about the axonal loss.

In the current study, RT, GCL, and RNFL measurements of patients diagnosed with mild and moderate dementia with probable AD were analyzed. Due to cooperation difficulties, patients with severe dementia with probable AD were not
included in the study. Because our study groups differed in age statistically and both eyes of patients were included whenever eligible, GLMM was used for intergroup analysis correcting results for age differences.

No significant difference was found between mild, moderate AD and control groups for grand mean, superior mean, and inferior mean RT and grand mean, superior mean, and inferior mean GCL measurements. For RT and GCL measurements, superior/inferior asymmetry and differences were analyzed among the groups in 5 different retinal zones. Superior retinal zone 2 and inferior retinal zone 2 had lower retinal thickness measurements in the mild and moderate AD group, but this was not statistically significant. Whereas GCL segmentation showed statistically significant thinning in the SZ-2 and the IZ-2 in moderate AD. Both SZ-2 and IZ-2 in mild AD had lower measurements than controls but not at the level of statistical significance. Superior/inferior asymmetries in the AD groups and controls did not differ between the groups. Both GCL thickness in SZ-2 and IZ-2 regions and GCL/RT ratio in the SZ-2 region were statistically significantly different.

With the zonal approach, superior and inferior zone 2 were affected significantly in the moderate AD group compared to the mild AD and control group. However, the GCL measurements in zone 2 were lower in the mild AD group than the control group but not statistically significant. This finding leads to consideration about the progressive loss of GCL in this zone. This zone may be a zone of focus as a possible biomarker for AD which we should consider to diagnose and follow up patients. Because we found superior and inferior Zone 2 were affected symmetrically and focally in moderate AD patients, we found no differential asymmetry among the groups.

Multiple regression analysis was used for the factors affecting the thickness loss in the superior and inferior zone 2. Age and moderate AD were important factors for SZ-2 and age was an important factor affecting IZ-2. Both moderate AD and age were found to be significant factors affecting GCC/RT in superior zone 2.

In the literature, Shao et al. reported a study including 25 AD, 24 mild cognitive impairment (MCI) and 21 cognitively normal control patients. They showed that ganglion cell-inner plexiform layer (GCIPL) in AD and MCI was thinner in superior, nasal superior, and temporal superior quadrants, compared to controls (p < 0.05) [19]. In the report by Cheung et al., including analysis of 100 AD cases, the most profound thinning was located in the superior nasal and superior sectors after full adjustments for confounding factors [20].

Choi et al. reported the most profound thinning of GCIPL in the inferior region in a study including 42 patients with AD, 26 with MCI, and 66 normal elderly controls. They reported the temporal RNFL thickness, the average, and minimum GCIPL thicknesses, and the GCIPL thickness in the inferonasal, inferior, and inferotemporal sectors at baseline was significantly reduced in MCI patients who were converting to AD compared to stable MCI patients [21].

Many studies showed decreased RNFL measurements in AD [9]. But the affected quadrants vary substantially between reports. In one meta-analysis, a significant reduction in the mean RNFL thickness was reported in AD patients compared with controls and subsequent analyses revealed that all quadrants were significantly thinner in AD patients, with the superior quadrant demonstrating the most significant reduction [8]. On the contrary, no decrease in mean RNFL measurements was found in our study, but interestingly superonasal quadrant was significantly thicker in moderate AD. In the literature, some other studies reported no difference in RNFL measurements in AD [22]. Golanz et al. reported that the average RNFL thickness across three groups, namely control subjects (n:50), preclinical AD (n:23) and clinical AD (n:23), did not differ significantly [23]. Haan et al. reported peripapillary RNFL and total retinal layer thicknesses were not significantly different between groups including 15 early-onset AD and 15 healthy controls [24]. Ferrari et al. reported significant global RNFL thinning in moderate AD but not mild AD patients compared to controls; thus, thinning of the RNFL may not occur until the disease progresses to higher stages of AD [25]. The reason why our results deviate from the vast majority of reports may be related to our strict inclusion criteria, as we did not include patients with glaucoma and optic neuropathy. Another reason may be related to different progression patterns of AD. As in the study reported by Haan et al. including early-onset AD subjects, no difference was found in RNFL measurements. But increases in the SN-RNFL measurement may reflect the gliotic process. Prospective studies with a larger number of patients are needed to clarify the disease process.

In the current study, IOP was lower in the moderate AD group. Some studies showed that decreased intracranial perfusion is associated with AD [26]. The decreased blood flow in patients with AD may be a contributing factor for lower IOP. In the current study, glaucoma patients were not included. Some studies showed increased glaucoma prevalence in AD. Both diseases may share common pathophysiologic mechanisms like decreased transcranial blood pressure. However, we aimed to characterize specific macular thickness and GCL changes associated with AD and did not include patients with glaucoma.

In the current study, retinal thickness and GCL were evaluated using posterior pole analysis and the macula was divided into 5 corresponding superior and inferior zones. Zone 1 was closest to the fovea and zone 2 represented the parafoveal zone. As GCL includes more than one layer of cells in this region, elucidating any pathologic process will be easier. Many other studies showed GCL changes, especially in superior and inferior macula. But we found two, specifically corresponding to superior and inferior zone 2, were affected locally. Further studies concentrating on these zonal approaches are needed to delineate if these local changes correlate with progression of AD and whether could it be a biomarker for AD.

Our study has some limitations. Firstly, the number of our study population is limited. We divide disease groups by MMSE and we did not include drug usage and disease duration in the analyzes. Moreover, AD is a disease of the elderly and coincides with an increased incidence of other systemic and ocular pathologies like senile macular degeneration and glaucoma. To investigate associated OCT changes some inclusion criteria were defined and we excluded some eyes that did not meet
the criteria at examination and others due to low-quality imaging. This helps us to deal with some intraocular confounding factors. But systemic confounding factors may have an effect. Another limitation of the current study is its cross-sectional design which is unable to show dynamic disease processes. However, we find GCL-SZ-2 and IZ-2 measurements consistently lower in moderate AD patients. We think that future studies about biomarkers of AD should be undertaken and investigate these zones to further support our research with larger cohorts.

In conclusion, by using posterior pole analysis which is designed to analyze superior-inferior retinal thickness asymmetry in glaucoma patients, we identified zone-2 which is mostly affected in AD. We found GCL thickness was significantly lower in the superior and inferior zone-2 in moderate AD when compared to mild AD and healthy controls. In the current study, the zonal approach was shown to be useful in the diagnosis and follow-up of AD patients.

Disclosure of any financial/other conflicts of interest

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