SUMMARY

Introduction/Objective The study aims to analyze the thickness of both the ganglion cell layer and the inner plexiform layer (GCL + IPL) among patients suffering from dry and wet form of age-related macular degeneration (AMD).

Methods One hundred ninety-five patients with AMD participated in the study, along with 94 healthy individuals (mean age 75.2 ± 7.8 years; range 55–86). They were divided into three groups: the first group, or group I, included 100 patients suffering from wet AMD; the second group, or group II, included 95 patients afflicted with dry AMD; the final 94 patients made up the control group, group III, of healthy individuals without systemic or ocular diseases. Measurements such as the average macular thickness, the average and minimum GCL + IPL thickness, and the GCL + IPL thickness in all six sectors were obtained by Cirrus spectral-domain optical coherence tomography (SD-OCT, Carl Zeiss Meditec, Inc., Dublin, CA, USA). SPSS version 20.0 was used to analyze the data, while the level of statistical significance was set at p < 0.05.

Results In the case of patients with wet AMD, the average value for GCL + IPL thickness was 43.13 μm, for patients with dry AMD the value was 66.73 μm, and the average thickness measured for the control group was 86.23 μm. There was a statistically significant difference between the average GCL + IPL and minimum GCL + IPL thicknesses between the groups (p < 0.001). Lower values were noted for patients with wet AMD (p < 0.001) than those with dry AMD. In the latter, the average GCL + IPL and the minimum GCL + IPL thicknesses were lower than those of the healthy participants, at a level of statistical significance (p < 0.001).

Conclusion Participants with AMD exhibited thinner GCL + IPL than the healthy participants, as did the participants with wet AMD when compared to the participants with dry AMD.

Keywords: dry AMD; wet AMD; ganglion cell layer; ganglion cell complex

INTRODUCTION

The onset of blindness in developed countries is frequently caused by age-related macular degeneration (AMD) [1, 2, 3]. The basic changes which lead to the disease mostly affect the outer retinal layers, the Bruch’s membrane, and the choriocapillaris. AMD leads to degeneration of the photoreceptors and retinal pigment epithelium of the macula [4–8]. The later stages of the disease can develop into geographic atrophy (GA) or neovascular AMD [9–14].

However, lately, any changes affecting the inner layers of the retina among patients suffering from AMD have been the focus of further study. Consequently, a great deal of importance has been paid to inner retinal layer analysis, especially to the ganglion cell complex (GCC), that is, the ganglion cell layer – or the inner plexiform layer (GCL + IPL) in particular. The layer can be obtained through segmentation, by using optical coherence tomography (OCT) [15].

The three layers contained within the inner retina make up the retinal ganglion cells complex. They include the following: the retinal nerve fiber layer (RNFL), encompassing the ganglion cell axons; the GCL, consisting of the ganglion cell bodies; and the IPL, made up of the ganglion cell dendrites [15]. The GCC is not necessarily solely limited to making differential diagnoses or managing glaucoma. It is important to note that its application extends to multiple neurological and retinal conditions [16, 17].

In clinical practice, an AMD diagnosis is usually made following an ophthalmoscopic examination of the macula, color fundus photography, an Amsler grid, visual field testing with automatic microperimetry in scotopic conditions, a test for the macular threshold, contrast-sensitivity, and fluorescein angiography [18, 19].
Another essential diagnostic tool is OCT. Its advantage is that it provides not only real-time, but also objective and reproducible retinal thickness measurements, as well as morphological measurements [20, 21]. In the detection of any structural damage to the retina, OCT is known to researchers as the gold standard. It also measures macular GCC thickness, which represents the combined thickness of RNFL, the GCL + IPL around the macula. The Cirrus spectral-domain optical coherence tomography (SD-OCT, Carl Zeiss Meditec, Inc., Dublin, CA, USA) incorporates the latest ganglion cell analysis algorithm, which precisely delineates only the macular GCL + IPL, excluding the RNFL. Therefore, any effect on the total GCC which could result from possible changes to the RNFL is precluded [22, 23, 24].

The purpose of this study was to analyze macular GCL + IPL thickness in patients with the dry and wet form of AMD. These values were compared to those obtained from measurements of a control group of patients, so as to assess any potential impact of AMD on the inner layers of the retina.

**METHODS**

A prospective, nonrandomized, observational monocentric study was conducted on 195 patients with AMD and 94 healthy persons between May 2016 and May 2017 at the Maja Clinic Special Hospital for Ophthalmology, Niš, Serbia. The study was approved by the Clinic Ethics Committee. The patients included in the study were divided into three groups: the first group, or group I, included 100 patients suffering from wet AMD; the second group, or group II, included 95 patients afflicted with dry AMD; the final 94 patients made up the control group, or group III, consisting of healthy patients without systemic or ocular diseases. After presenting at the Clinic, the participants with noted AMD were enrolled consecutively; the control group was recruited from a population of normal, healthy, sex- and age-matched individuals. The implemented procedure followed the tenets of the Declaration of Helsinki. Each patient provided informed consent following an explanation of the nature of the study, and any possible consequences thereof.

The inclusion criteria were as follows: age over 55 years and retinal changes classified as stages of the AMD. Patients with end-stage disease, GA, and end-stage AMD were excluded from the study.

The exclusion criteria included the following: any ocular disease with a possible confounding effect on the assessment of the retina, except AMD (retinal vessel occlusion, glaucoma, diabetic retinopathy, retinal dystrophies, and uveitis), as well as any previous or any concomitant therapy the patient might have been undergoing to treat their AMD (intravitreal steroids, anti-vascular endothelial growth factor, ocular surgery, laser coagulation etc.). In addition, patients with any neurologic disease were excluded from the study.

The study procedures included a baseline visit, followed by regular study visits, and a full ophthalmic and fundus examination, including multimodal retinal imaging as required by standard operating procedures. These procedures required the use of a Cirrus SD-OCT device (model 4000, software version 6.0). The thickness of the macular GCL + IPL was measured using the ganglion cell analysis algorithm included in the aforementioned device. The following measurements were taken: the average and minimum thickness of the GCL + IPL, along with the thickness of the six sectors (superotemporal, superior, superonasal, inferonasal, inferior, inferotemporal) starting from the elliptical annulus which is centered on the fovea. Macular image acquisition was obtained once mydriasis was achieved following the administration of 1% tropicamide eye drops. The data collected from the healthy patients were also analyzed. They were subject to the following criteria: (1) no ocular pathology, (2) no history of ocular surgery including intravitreal injections, (3) normal computerized visual field – standard automated perimetry finding [24–2 Swedish Interactive Threshold Algorithm (SITA), Humphrey Field Analyzer II, Carl Zeiss Meditec], (4) intraocular pressure ≤ 21 mmHg measured by Goldmann applanation tonometer, (5) no systemic or/and neurological disease, and (6) best-corrected visual acuity 20/20, and refractive error within ± 0.5 D.

Following the baseline visit, the control group of healthy participants needed to return for a follow-up visit after one year. Since the study is longitudinal, in order for the data from the control group to be included in the analysis, the participants needed to complete at least two visits over the span of a single year.

**Statistical analysis**

We classified the eyes into three groups based on their clinical pattern: neovascular (wet) AMD, dry AMD, and control subjects. Kruskal–Wallis and Man–Whitney nonparametric statistical tests for independent data were used to compare the value of GCL + IPL in neovascular (wet) and dry AMD and in the control group. The quantitative values calculated in the study were expressed as means and standard deviations. The level of statistical significance for the statistical calculations was set at p < 0.05. The confidence interval was set at 95%. IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used for all the data analyses.

**RESULTS**

One hundred eyes of 100 patients (mean age at presentation 75.2 ± 7.8 years, range 55–86 years; male vs. female 51/49) with signs of wet AMD from the base of our OCT study were compared with 95 patients with dry AMD (mean age 70.1 ± 7.1 years, range 55–83 years; male vs. female 48/47). The control group comprised 94 age- and sex-matched patients (mean age 73.3 ± 7.3, range 55–85 years; male vs. female 47/47). The necessary demarcation of the superior sectors was done from the nasal to the temporal sector. Consequently, the superior nasal sector of GCL + IPL was marked GC1, the superior one GC2.
and the superior-temporal one GC3. The demarcation of the inferior sectors was also done from the temporal to the nasal sector, which meant that the inferior temporal sector was marked GC4, the inferior one GC5, and the inferior-nasal one GC6.

The Kruskal–Wallis nonparametric statistical test showed a statistically significant difference for the individual thickness of each segment of the GC complex (GC1–GC6) between the three groups (p < 0.001) — wet AMD, dry AMD, and the control group of healthy patients. By using the Mann–Whitney tests we demonstrated that separate thicknesses of sectors GC1–GC6 were higher in healthy patients (p < 0.001) than in both AMD groups, as well as in the group of dry AMD patients than in the wet AMD (p < 0.001) group — the detailed values are reported in Table 1. As indicated, the control group had a thicker average GCL (86.23 μm), the dry AMD group had a thickness of 66.73 μm, and the wet AMD group had a thickness of 43.13 μm.

A statistically significant difference was noted between the values for average GCL + IPL between the groups (p < 0.001). It was thinner in patients with wet AMD (p < 0.001) than inthose with dry AMD. A statistically significant difference was noted between the values of average GCL + IPL for the dry AMD group and the group of healthy patients (p < 0.001).

Statistically significant differences between the groups were also determined for minimum GCL + IPL thickness (p < 0.001). The results indicated it was thinner among the patients of the wet AMD group (p < 0.001) than among the patients of the dry AMD group. A statistically significant difference for minimum GCL + IPL was noted between the patients of the dry AMD group and the healthy group of patients (p < 0.001), with lower thickness recorded for the former.

A statistically significant difference for central foveal thickness was noted for all three groups. The lowest thickness was noted for the dry AMD group, 195.94 μm, followed by the control group — 255.43 μm, and the greatest thickness was noted in patients with wet AMD — 292.07 μm.

Table 1. Mean ganglion cell layer and inner plexiform layer (μm) in wet, dry age-related macular degeneration and control subjects

| Sector of GCL + IPL | AMD wet n = 100 | AMD dry n = 95 | Control subjects n = 94 | p |
|---------------------|----------------|----------------|------------------------|---|
| GC1                 | 44.47          | 67.55          | 86.34                  | < 0.001 |
| GC2                 | 42.76          | 64.7           | 86.55                  | < 0.001 |
| GC3                 | 43.46          | 66.1           | 86.45                  | < 0.001 |
| GC4                 | 43.26          | 66.38          | 86.12                  | < 0.001 |
| GC5                 | 44.38          | 66.13          | 86.62                  | < 0.001 |
| GC6                 | 42.04          | 67.55          | 86.31                  | < 0.001 |
| GCL avg.            | 43.13          | 66.73          | 86.23                  | < 0.001 |
| GCL min.            | 40.03          | 60.57          | 82.49                  | < 0.001 |
| CFT                 | 292.07         | 195.94         | 255.43                 | < 0.001 |

GCL + IPL – ganglion cell layer and inner plexiform layer; GC1 – superior nasal sector of GCL + IPL; GC2 – superior sector of GCL + IPL; GC3 – superior-temporal sector of GCL + IPL; GC4 – inferior temporal sector of GCL + IPL; GC5 – inferior sector of GCL + IPL; GC6 – inferior-nasal sector of GCL + IPL; GCL avg. – ganglion cell layer and inner plexiform layer average; GCL min. – ganglion cell layer and inner plexiform layer minimum; CFT – central foveal thickness

**DISCUSSION**

The introduction of OCT started a revolution in the research on inner retinal layers in patients with AMD. Special attention had to be focused on three layers: the IPL, the GCL, and the RNFL, which form the GCC [2, 21]. Software upgrades for the SD-OCT systems have been developed and made available to the public to keep up with the progress of research into the thickness of the GCL [22].

The segmentation of the GCC, which allows researchers to measure the thickness of this section alone, as well as track any thickness changes that take place over time, enabled them to recognize the importance of GCC when establishing diagnoses and monitoring any changes that occur in patients afflicted with various diseases of the retina, the macula, and the optic nerve. The importance of GCC segmentation and the need to perform it have been proven in multiple studies [23, 24]. It is now possible to segment the macular GCL + IPL, with the exclusion of the remaining RNFL, by using the ganglion cell analysis algorithm which is now a constituent part of the Cirrus HD-OCT (Cirrus Version 6.0) [25]. Consequently, any changes to the RNFL will not affect the entire GCC.

So far, only a few studies have investigated GCC + IPL thickness in AMD. Zucchiatti et al. [26] investigated exactly the same GCL + IPL as we did. Their results showed that mean GCC thickness was higher in the control group (79.9 ± 5.5 μm), becoming progressively thinner in advanced AMD forms (neovascular AMD had a mean GCC thickness of 53.8 ± 16.9 μm while atrophic AMD had a mean of 50.4 ± 17.9 μm). Compared to the results of our study, the values of GCC thickness are almost the same.

It is also of great importance to monitor the changes in GCL + IPL thickness after multiple anti-vascular endothelial growth factor (anti-VEGF) therapy treatments to observe if there is an additional reduction in thickness of this layer, or whether anti-VEGF therapy does not adversely affect GCL + IPL thickness. There are a few studies investigating the effect of intravitreal anti-VEGF injections on RNFL and GCC, but the results are controversial [27, 28]. It is important to point out that the GCL + IPL layer is thinned out by the disease itself before any application of the VEGF treatment and it should be analyzed among patients whose visual acuity did not improve despite aggressive anti-VEGF treatment. Further studies should focus on the investigation of GCL + IPL thickness after multiple applications of anti-VEGF treatment.

Patients with dry AMD are expected to have thinner GCL + IPL compared to patients with wet AMD, which was not confirmed in this study. More studies are required for a better understanding of retinal structural changes in neovascular AMD that occur as a consequence of the natural course of the disease.

Lee et al. [29], analyzing the GCL + IPL and RNFL among patients with dry AMD, reached the conclusion that in this particular case, the thickness of the GCL + IPL and the RNFL were not as high as those measured in control eyes. The results of this study also indicate that there is a negative correlation between the thickness of...
the average GCL + IPL and the drusen area. In addition, patients suffering from GA, caused by AMD, experience significant GCL loss [30]. In the aforementioned study, the authors were able to conclude that ganglion cell death could be followed by axonal loss, and that increased macular RNFL volumes are not indicative of GCL volume [30].

Borelli et al. [31] analyzed the GCC of 68 eyes with intermediate AMD which exhibited GCC thinning (the average and minimum GCC thicknesses were thinner in AMD patients than in healthy controls (69.54 ± 9.30 μm and 78.57 ± 6.28 μm, respectively), which supports the concept of postreceptor retinal neuronal loss as a contributing factor to retinal thinning in intermediate AMD.

It is important to point out that the presence of thinning not only in GCL + IPL but also in RNFL imposes the following question: how are the structural changes in patients with both glaucoma and AMD supposed to be followed, since both diseases result in the thinning of both GCL + IPL and RNFL. Rimayanti et al. [32] concluded that there is damage to the inner retinal layers in eyes with AMD. Even if this is not the topic of interest in our current study, it is useful to have in mind that RNFL thickness significantly correlates with glaucoma in AMD eyes. RNFL thickness can be a useful parameter for differentiating eyes with AMD from eyes with both AMD and glaucoma [32].

CONCLUSION

Changes to the inner macular layer are a consequence of both dry and wet AMD. These changes take the form of a reduction in the thickness of the macular GCL + IPL. Patients with cases of wet AMD have a thinner GCL + IPL compared to patients with cases of dry AMD. This excludes any patients suffering from GA.

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An earlier version of the manuscript has been presented as an abstract at the Congress of the European Society of Ophthalmology (SOE) 2017, according to the following link: http://www.professionalabstracts.com/soe2017/eBook/#0

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САЖЕТАК

Увод/Циљ

Циљ студије је био да се анализирају промене дебљине слоја ганглијских ћелија и унутрашњег плексиформног слоја код болесника са сенилном дегенерацијом жуте мрље.

Метод

Студија је спроведена на 195 болесника са сенилном дегенерацијом жуте мрље и 94 здраве особе (средња старосна доба 75,2 ± 7,8 година; опсег 55–86 година). Болесници су подељени у три групе: група I – 100 болесника са влажном формом СДМ, II група – 95 болесника са сувом формом СДМ и III група – 94 здраве особе. Испитивање је вршено помоћу Cirrus SD-OCT (Carl Zeiss Meditec, Inc., Даблин, Калифорнија, САД). Мерене су просечна и минимална дебљине СГЋ + УПС у свим шест сектора. Статистичка анализа извршена је коришћењем SPSS верзије 20.0 применом одговарајућих статистичких метода. Вредност р < 0,05 се сматрала статистички значајним резултатом.

Резултати

Просечна дебљина СГЋ + УПС код болесника са влажном формом СДМ износила је 43,13 μm, код болесника са сувом формом СДМ била је 66,73 μm, а код здраве особе 86,23 μm. Просечне и минималне дебљине СГЋ + УПС статистички значајно разликују између група (р < 0,001) и биле су тање у влажној форми СДМ (р < 0,001) него код здраве особе. У групи суве форме СДМ, просечна дебљина СГЋ + УПС и минимална дебљина СГЋ + УПС су статистички значајни разликују код здраве особе (р < 0,001).

Закључак

СДМ одликује истањење СГЋ + УПС. Болесници са влажном формом СДМ имају тањи СГЋ + УПС у поређењу са болесницима са сувом формом СДМ.

Кључне речи: СДМ, СГЋ + УПС, просечна дебљина, минимална дебљина.