Effect of age and sex on retinal layer thickness and volume in normal eyes

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Abstract
The aim of the study was to evaluate the effect of sex and age on the thickness of the retinal layer in normal eyes using spectral-domain optical coherence tomography (SD-OCT).

Fifty healthy subjects between the ages of 20 and 80 had their retinal layers measured using SD-OCT at Seoul St. Mary’s Hospital. Mean thickness and volume were measured for 9 retinal layers in the fovea, the pericentral ring, and the peripheral ring. The differences of sex- and age-related thickness and volume in each retinal layer were analyzed.

The retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), and outer plexiform layer (OPL) were thinnest in the fovea area, whereas the outer nuclear layer (ONL), photoreceptor layer (PHL), and retinal pigment epithelium (RPE) were thickest at similar locations. Mean thickness of the RNFL, GCL, IPL, and OPL was significantly greater in men than women. However, mean thickness of the ONL was greater in women than in men. When compared between patients < 30 years and > 60 years of age, the thickness and volume of peripheral RNFL, GCL, and pericentral and peripheral IPL were significantly larger in the younger group than the older group. Conversely, the thickness and volume of foveal INL and IR were larger in the older group than in the younger group.

The thickness and volume of the retinal layer in normal eyes significantly vary depending on age and sex. These results should be considered when evaluating layer analysis in retinal disease.

Abbreviations: BCVA = best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, GCL = ganglion cell layer, INL = inner nuclear layer, IPL = inner plexiform layer, IR = inner retina, ONL = outer nuclear layer, OPL = outer plexiform layer, PHL = photoreceptor layer, RNFL = retinal nerve fiber layer, RPE = retinal pigment epithelium, SD-OCT = spectral-domain optical coherence tomography.

Keywords: age, retinal layer thickness, retinal layer volume, sex, spectral-domain optical coherence tomography

1. Introduction
The analysis of individual retinal layers is important to diagnose retinal disease and verify therapeutic response. Several previous studies have demonstrated the thickness of retinal layers in normal eyes and revealed regional differences in macular thickness according to age, sex, and axial length changes.\(^{1-3}\)

Optical coherence tomography (OCT) software development has enabled automatic segmentation of the retinal layers. Ooto et al\(^{4}\) have demonstrated changes in individual retinal layer thickness according to age in the eyes of a Japanese population by an automated layer segmentation algorithm. Because specific layers among the retina are affected in some retinal diseases, examining the involved layers by OCT imaging allows clinicians to confirm improvement or progression of retinal disease. For example, previous studies using ultra-high resolution OCT showed that the severity of photoreceptor loss is associated with visual loss in retinitis pigmentosa.\(^{5,6}\) Other studies using spectral-domain (SD) OCT showed that the thickness of the outer nuclear layer in the fovea is associated with visual acuity in retinal diseases such as central serous chorioretinopathy, polypoidal choroidal vasculopathy, and epiretinal membrane.\(^{7-11}\)

Most recently, updated software for SD-OCT was introduced with a new transverse section analysis for positioning and quantifying retinal diseases with automated measurement of macular thickness, in addition to automated segmentation of the retina into individual layers. The retina could not be segmented into the 9 retinal layers in previous studies. Thus, this study is the first to report automated retinal segmentation, and measure the thickness and volume of 9 macular individual layers using the OCT program, especially distinguishing between the outer plexiform layer and outer nuclear layer. The purpose of this study is to evaluate sex-related differences and age-related changes in thickness and volume of the 9 individual retinal layers in the normal eye, using SD-OCT with HEYEX 6.0C software (Heidelberg Engineering, Heidelberg, Germany).

2. Methods
2.1. Subjects
The medical charts of 50 healthy Korean subjects enrolled at Seoul St. Mary’s Hospital between January 2014 and October 2015 were reviewed. This study was conducted according to the
guidelines of the Association for Research in Vision and Ophthalmology. It adheres to the tenets of the Declaration of Helsinki and all protocols were approved by the Institutional Review Board of the Catholic University of Korea. Ophthalmologically healthy Korean subjects between the ages of 20 and 80 were recruited for this study. Exclusion criteria included any ocular disease or systemic disease including diabetes, hypertension, autoimmune, multiple sclerosis, rheumatoid arthritis or infectious diseases, such as HIV. Initial ocular examinations included best-corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure measurement, auto refractometry, keratometry, and funduscopy to rule out any glaucoma or retinal diseases.

Exclusion criteria included BCVA worse than 20/25, refractive error over +5.0 or over −6.0 diopters, intraocular pressure >21 mm Hg, abnormal fundus findings, significant media opacities, history of intraocular surgery, findings of vitreo-retinal disease, and systemic disease, including diabetes mellitus, that could affect the eye. All subjects received an eye drop consisting of 0.5% tropicamide combined with 0.5% phenylephrine (Mydrin-P, Santen, Osaka, Japan) for pupil dilation. SD-OCT images were obtained using a commercially available OCT instrument (SPECTRALIS, Heidelberg Engineering, Germany) operated by a single experienced examiner.

2.2. SD-OCT measurements

OCT images then underwent automated segmentation of individual retinal layers: retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), inner retina (IR, from internal limiting membrane to external limiting membrane), photoreceptor layer (PHL), and retinal pigment epithelium (RPE)\(^8\) (Fig. 1). In this study, 3 retinal areas were demonstrated according to this Early Treatment Diabetic Retinopathy Study (ETDRS) grid: the fovea, the central circle with a diameter of 1 mm; the pericentral ring, 1 to 3 mm from the center of the fovea; and the peripheral ring, 3 to 6 mm from the center of the fovea (Fig. 2). Automated measurement of their mean macular thickness and volume was done in 9 separate areas based on ETDRS sectors. The mean macular thickness and volume of each retinal layer was measured at the fovea and 4 sectors (superior, inferior, nasal, and temporal) of the pericentral and peripheral rings. The mean thicknesses of the pericentral and peripheral rings were measured by averaging the thickness measurements of the 4 corresponding quadrant areas (segments 2 to 5 for the pericentral ring and segments 6 to 9 for the peripheral ring). Total macular thickness of all areas within the ETDRS grid was automatically calculated by summation of the 9 sectors.
Table 1
Demographics and ocular features of subjects.

| Characteristic | Mean ± SD |
|----------------|-----------|
| OD/OS, N       | 25±25     |
| Men:women, N   | 24±26     |
| Age, y         | 48.64±14.9|
| Mean refractive error, diopters | -2.17±3.18 |
| IOP, mm Hg     | 14.3±0.11 |
| BCVA, log MAR   | 0±0.11    |

BCVA = best-corrected visual acuity, IOP = intraocular pressure, SD = standard deviation.

2.3. Statistical analysis

Statistical data were analyzed with a statistical software program (IBM SPSS 21; SPSS Inc. Chicago, IL). A P-value <0.05 was considered statistically significant.

An independent sample t-test was used for comparing macular layer thickness between the younger age group (<30 years) and the older age group (>60 years). For analyzing sex-associated differences and comparing retinal thicknesses among the sectors, an independent sample t-test was used.

3. Results

Mean thickness of the individual retinal layers in the 9 ETDRS sectors is shown in Table 2.

As shown in Table 2, the RNFL, GCL, IPL, INL, and OPL were thinnest in the foveal area, whereas the OPL, PHL, and RPE were thickest. In the pericentral and peripheral rings, the RNFL and GCL were thicker in the nasal quadrants than in the temporal quadrants. The RNFL was thickest in the peripheral retinal area, especially from nasal to the fovea and near the optic nerve head. The GCL was thickest in the pericentral area. The IPL was thicker in the pericentral ring than the peripheral ring, with a relatively similar thickness in the 4 pericentral sectors. The INL and OPL were thinner in the pericentral ring than the peripheral ring. The ONL was thickest in the central fovea area and decreased in peripheral retinal areas. The thicknesses of the PHL and RPE were increased in the central fovea area compared to the other sectors.

Mean thickness of the RNFL, GCL, IPL, IR in all ETDRS sectors, INL and OPL in the fovea, and OPL in the pericentral ring was significantly greater in men than in women, whereas mean thickness of the ONL was greater in women (Table 3). This finding is quite different from the previous study by Ooto et al.[14] They reported that the mean RNFL thickness was significantly greater in women than in men, especially at the peripheral macula.

When macular thickness was compared between <30 years and >60 years of age, peripheral RNFL, peripheral GCL, and pericentral and peripheral IPL were significantly thicker in the younger age group than the older age group. On the other hand, fovea INL and fovea IR were thicker in the older age group than in the younger group (Table 4).

With regard to macular volume, peripheral RNFL and peripheral IPL were significantly greater in the older age group than in the older age group. Conversely, peripheral GCL, fovea INL, and fovea IR were greater in the younger age group (Table 5).

4. Discussion

To date, there have been several previous studies about automated segmentation of individual retinal layers and measurement of macular thickness in the normal population. The automated retinal segmentation algorithm adopted by SD-OCT (SPECTRALIS, Heidelberg Engineering, Germany) has been used on mice.[13] However, to our knowledge, this study is the first report to differentiate the OPL and ONL layers automatically by the OCT program itself, and carry out segmentation with thickness and volume into 9 retinal layers in human. In several previous studies, the thicknesses of the RNFL, GCL, IPL, and INL were so thin that they could not be reliably measured,[14] and the segmentation of the macular layer into 6 or 7 retinal layers (OPL+ONL as 1 or lack of an RPE layer), rather than 9 individual layers, was performed.[14]

The OCT-based mean thickness data of individual retinal layers in our study is similar to other previous reported SD-OCT studies, except for some differences that can be attributed to variances in the population of study, kind of OCT devices, and the differences in segmentation algorithms in detecting the posterior retinal boundary.[15–17]

Several previous studies showed that total retinal thickness in the nasal quadrant is greater than in the temporal quadrant, and is greater in the pericentral ring than the peripheral ring.[13–23]

These results were also similar in our study. However, on closer examination, the GCL and INL were thinner in the temporal sector than in the nasal sector within the pericentral ring, but this difference was smaller within the peripheral ring. We also found that there may be a correlation between INL and

Table 2
Mean layer thickness measurements (μm) of the individual retinal layers of subjects in the 9 ETDRS sectors.

| Retinal layer | Fovea | Pericentral ring | Peripheral ring |
|---------------|-------|------------------|-----------------|
|               | Superior | Temporal | Inferior | Nasal | Superior | Temporal | Inferior | Nasal |
| RNFL          | 11.5±2.5 | 24.5±2.5 | 17.4±1.3 | 25.6±2.6 | 20.6±0.8 | 38.0±4.9 | 20.2±4.5 | 41.6±6.9 | 46.4±7.0 |
| GCL           | 12.6±3.2 | 52.1±4.8 | 46.3±5.6 | 51.7±4.6 | 50.8±4.8 | 36.2±3.6 | 37.3±5.3 | 33.2±3.3 | 39.9±3.1 |
| IPL           | 19.2±3.1 | 41.0±2.9 | 40.1±3.0 | 40.7±2.8 | 42.1±3.4 | 29.3±2.6 | 33.5±3.1 | 26.8±2.4 | 30.8±2.4 |
| INL           | 16.4±4.4 | 40.4±3.2 | 37.8±3.2 | 39.9±3.1 | 39.6±3.6 | 32.7±2.5 | 34.1±2.5 | 31.2±2.7 | 34.7±2.5 |
| OPL           | 23.7±7.9 | 58.0±4.7 | 31.4±4.7 | 34.3±11.0 | 34.1±7.3 | 28.2±3.8 | 27.4±2.1 | 26.9±3.1 | 29.7±3.0 |
| OPL           | 96.1±11.5 | 66.6±14.0 | 74.3±9.3 | 66.9±12.8 | 73.7±12.2 | 90.0±7.2 | 59.0±6.2 | 52.3±6.5 | 58.6±7.9 |
| INL           | 90.3±4.8 | 82.9±3.1 | 83.1±2.9 | 80.9±3.1 | 83.6±5.0 | 79.7±2.9 | 79.0±3.0 | 77.6±3.1 | 79.5±2.6 |
| OPL           | 16.8±1.8 | 15.4±2.0 | 14.6±1.4 | 14.4±1.9 | 15.2±1.8 | 13.3±1.7 | 12.9±1.4 | 12.8±1.6 | 13.4±1.5 |
| Total         | 268.6±19.1 | 345.5±12.6 | 330.3±11.3 | 339.4±0.9 | 344.4±12.4 | 304.5±12.0 | 290.8±14.4 | 289.7±12.6 | 319.4±12.4 |

Note: ETDRS = Early Treatment Diabetic Retinopathy Study, GCL = ganglion cell layer, INL = inner nuclear layer, IPL = inner plexiform layer, ONL = outer nuclear layer, OPL = outer plexiform layer, PHL = photoreceptor layer, RNFL = retinal nerve fiber layer, RPE = retinal pigment epithelium.
GCL as the maximum thickness of INL and GCL both occurred in the same quadrant areas. Thus, we can assume that the densities of bipolar cells, amacrine cells, horizontal cells, and Muller cells are likely high in these areas.

In our study, mean macular thickness of the RNFL, GCL, IPL, ONL, and INL were thinnest in the central fovea area, as expected with normal anatomy. The RNFL thickness was highest in the peripheral retinal area near the optic nerve head, because of the high density of local nerve fiber bundles. Our study also presented that the GCL thickness correlates with peripapillary RNFL thickness, as in other studies. The ONL and PHL displayed a maximum thickness in the central fovea area as expected in normal anatomy, partially because of the elongation of cone photoreceptors at the fovea.

Previous studies have shown sex-related differences in total macular thickness or in thicknesses of some sectors. In earlier work, the mean total retinal thickness at the central fovea was significantly greater in men than in women, and mean retinal
Table 5
Differences in mean macular layer volume based on age.

| Macular layer | <30 y | >60 y | P* | Macular layer | <30 y | >60 y | P* |
|---------------|-------|-------|----|---------------|-------|-------|----|
| RNFL Fovea    | 0.01±0 | 0.01±0 | 1.0| OPL Fovea     | 0.022±0.006 | 0.022±0.007 | 0.89|
| Peripheral ring | 0.035±0.003 | 0.035±0.003 | 1.0| Peripheral ring | 0.055±0.1 | 0.056±0.007 | 0.77|
| Peripheral GCL | 0.207±0.018 | 0.187±0.016 | 0.01* | Peripheral ONL | 0.145±0.012 | 0.151±0.008 | 0.15|
| Fovea         | 0.01±0 | 0.01±0 | 1.0| Fovea         | 0.072±0.009 | 0.075±0.009 | 0.39|
| Peripheral ring | 0.081±0.005 | 0.079±0.004 | 0.18| Peripheral ring | 0.108±0.014 | 0.108±0.018 | 0.98|
| Peripheral PL | 0.079±0.019 | 0.186±0.011 | 0.04* | Peripheral PHL | 0.292±0.035 | 0.298±0.028 | 0.64|
| Fovea         | 0.015±0.005 | 0.016±0.005 | 0.70| Fovea         | 0.072±0.004 | 0.07±0.004 | 0.19|
| Peripheral ring | 0.066±0.005 | 0.064±0.004 | 0.28| Peripheral ring | 0.129±0.005 | 0.129±0.005 | 0.84|
| Peripheral INL | 0.161±0.015 | 0.156±0.006 | 0.02* | Peripheral RPE | 0.413±0.017 | 0.418±0.014 | 0.43|
| Fovea         | 0.012±0.004 | 0.014±0.005 | 0.015* | Fovea         | 0.012±0.004 | 0.011±0.003 | 0.48|
| Peripheral ring | 0.062±0.005 | 0.062±0.005 | 0.83| Peripheral ring | 0.022±0.003 | 0.023±0.004 | 0.68|
| Peripheral R | 0.178±0.011 | 0.170±0.014 | 0.13| Peripheral R | 0.005±0.007 | 0.070±0.009 | 0.14|
| Fovea         | 0.134±0.006 | 0.15±0.015 | 0.03* | Fovea         | 0.040±0.011 | 0.404±0.017 | 0.78|
| Peripheral ring | 0.406±0.011 | 0.404±0.017 | 0.78| Peripheral ring | 1.188±0.056 | 1.147±0.051 | 0.08|

GCL = ganglion cell layer, INL = inner nuclear layer, PL = inner plexiform layer, R = inner retina, ONL = outer nuclear layer, OPL = outer plexiform layer, PHL = photoreceptor layer, RNFL = retinal nerve fiber layer, RPE = retinal pigment epithelium.

Unpaired t-test (*); significantly different, P < 0.05.

thicknesses in all quadrants of the pericentral ring and in the temporal quadrant of the peripheral ring were significantly greater in men than in women.[5,24] In another study, the mean thicknesses of the INL and OPL+ONL were significantly greater in men than in women, but the mean RNFL thickness was greater in women than in men, especially at the peripheral ring. Therefore, because the RNFL is relatively thin, the authors suggested that differences of thickness in the INL and OPL+ONL may be predominately responsible for the sex-related thickness difference of the total retina in the central sector, pericentral ring, and temporal quadrant of the peripheral ring.[5] These results were partially similar with those in our study. However compared to previous studies, we were able to measure sex-related thickness differences in more individual retinal layers and found the mean thickness of the RNFL, GCL, IPL in all ETDRS sectors, foveal INL, foveal OPL, and OPL of pericentral ring was significantly greater in men than in women; conversely, the mean thickness of the ONL was greater in women (Table 3).

We found significant differences in thickness and volume of the retinal layer with age in a healthy population. When macular thickness was compared between < 30 years of age and >60 years of age, peripheral RNFL, peripheral GCL, and pericentral and peripheral IPL were significantly thicker in the younger age group than in the older age group (Table 4). Several previous histological studies support these results. The GCL and their axons (RNFL) are particularly prone to loss with age.[30,31] Additionally, in a previous study by Ooto et al,[6] the thicknesses in the RNFL, GCL, IPL, INL, and inner segment of the PHL were negatively correlated with age. However, the thickness of the OPL+ONL was unrelated with age, and the thickness of the outer segment of PHL had a positive correlation with age. Macular RNFL and GCL thickness also presented a linear correlation with negative slopes of −0.05 and −0.07 μm/year with age, respectively. And, like the results of our study, the decrease in thickness with age in other inner retinal layers (IPL and INL) suggests that aging is related to the loss of other neurons or glial cells in the INL. Indeed, several studies showed that aging was related with loss of neurons in the inner retina.[32,33] Also, histologic studies presented age-related losses of the retina as 0.3% to 0.6% per year, whereas the thickness of the RNFL decreases with age at a lower rate of 0.2% per year.[32,33] According to a previous study, structural changes of the RPE occur with age, including loss of melanin granules, accumulation of lipofuscin, basal deposits, and thickened Bruch’s membrane. Because of these, fovea RPE thickness can increase significantly with age.[12] In our study, however, foveal RPE thickness showed no significant differences with increasing age. This is likely due to differences in race and the type of OCT.

5. Conclusions
This study shows that there are differences in the thickness and volume of several retinal layers due to age and sex. Therefore, while analyzing retinal layer thickness associated with disease, these findings should be taken into consideration. Further research with more subjects would help shape these age-related changes and sex-related differences in thickness and volume of the retinal layer as more objective clinical parameters.

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