Determinants of Macular Ganglion Cell–Inner Plexiform Layer Thickness in Normal Chinese Adults

Xiaoyu Xu

Sun Yat-Sen University Zhongshan Ophthalmic Center <https://orcid.org/0000-0001-9511-8471>

Hui Xiao

Sun Yat-Sen University Zhongshan Ophthalmic Center

Kunbei Lai

Sun Yat-Sen University Zhongshan Ophthalmic Center

Xinxing Guo

Sun Yat-Sen University Zhongshan Ophthalmic Center

Jingyi Luo

Sun Yat-Sen University Zhongshan Ophthalmic Center

Xing Liu (✉ drliuxing@163.com)

<https://orcid.org/0000-0002-5498-2279>

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Abstract

Background

To determine the influences of multiple demographic and ocular factors on the measurements of macular ganglion cell–inner plexiform layer (GCIPL) thickness in normal Chinese adults.

Methods

This was a retrospective study conducted on 225 normal eyes from 225 healthy Chinese adults. GCIPL thickness were obtained using Cirrus high-definition optical coherence tomography (OCT). The age, gender, laterality, spherical equivalent (SE) refractive error, intraocular pressure (IOP), axial length (AL), central cornea thickness (CCT), circumpapillary retinal nerve fibre layer (pRNFL) thickness and OCT signal strength were recorded and their respective effect on GCIPL thickness parameters were evaluated.

Results

The mean ($\pm$ SD) average, minimum, superotemporal, superior, superonasal, inferonasal, inferior, and inferotemporal GCIPL thickness was (84.56 ± 5.36), (81.32 ± 5.58), (83.08 ± 5.37), (85.70 ± 5.95), (87.15 ± 6.26), (85.07 ± 6.11), (82.46 ± 5.76), and (83.88 ± 5.59) μm , respectively. Determinants of thinner GCIPL thickness were older age ($P = 0.001$ – 0.117 ; effects enhanced if age over 40 years), thinner pRNFL (all $P < 0.001$), and weaker signal strength (all $P < 0.001$). No significant difference was found between males and females ($P = 0.069$ – 0.842), and between right eyes and the left eyes ($P = 0.160$ – 0.875) except that of superonasal GCIPL thickness ($P < 0.001$). There was no significant correlation between GCIPL thickness and SE, IOP, CCT, and AL ($P = 0.135$ – 0.968).

Conclusions

Individual determinants associated with thinner GCIPL thickness were older age (particularly over 40 years of age), thinner pRNFL, and weaker OCT signal strength. This is relevant in comprehensively understanding the normative data and differentiating normal aging from abnormalities.

Background

As the output neurons of the retina, retinal ganglion cells (RGCs) are the only part of the central nervous system that can be optically detected *in vivo*.⁽¹⁾ The hallmark of glaucoma, one of the leading causes of irreversible blindness worldwide, is progressive loss of RGCs in the inner retina and their axons in the optic nerve head (ONH).⁽²⁾ Previous studies showed that structural glaucomatous changes primarily affect RGCs and their axons, followed by functional changes featured by characteristic glaucomatous visual field defect.^(3, 4) There may be a 20–40% of RGC loss prior to detectable visual field defect,^(5, 6) which indicates that early detection and monitoring of glaucoma could be benefit from the detailed evaluation of RGCs. The human retina contains an estimate of more than 1 million RGCs, over 50% of which are located in the macula.⁽⁷⁾ The high density of the RGCs makes the macula the easiest region for calculating the RGC counts and detecting their loss. The thinning

of macular ganglion cell layer (GCL) and peripapillary retinal nerve fiber layer (pRNFL) has been well recognized as biomarkers of optic nerve damage, which can be measured by optical coherence tomography (OCT) quantitatively in a non-invasive, precise, and reproducible way.

A number of studies have showed that the macular ganglion cell complex (GCC, the sum of RNFL, GCL, and inner plexiform layer) thickness, or the macular ganglion cell–inner plexiform layer (GCIPL) thickness has similar glaucoma discriminating performance with that of pRNFL.(8–13) Combining the measurements of GCC/GCIPL and pRNFL with optic disc parameters as well as psychophysics examinations and vasculature evaluations can help to improve the overall glaucomatous diagnostic ability and accuracy.(14, 15)

For clinical interpretation of GCC/GCIPL and pRNFL thickness readings, it is essential to know physiological factors that could influence the measurements. In normal eyes, age, sex, race, refractive power, axial length, optic disc size, and signal strength of OCT scanning are proven to be associated with GCC/GCIPL and/or pRNFL thickness; among these, the age is considered the most significant determinant by multiple studies.(16–24) However, some of the previous studies investigated multiple potential determinants with limited analysis deep into each determinant, and some emphasized on one or two determinants. Thus, an overall “big picture” is needed for better understanding which factors are impacting the OCT readings, how much the impacts are, and which should be taken into account in clinical interpretations despite normative database is used as a reference. The purpose of this study was to examine the influences of multiple demographic and ocular factors on the measurements of macular GCIPL thickness using Cirrus high-definition optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA) in a cohort of normal Chinese adults with detailed, comprehensive analyses.

Methods

In this retrospective observational study, all participants were consecutively recruited from the Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China, from February 2013 to January 2016. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB). Written informed consent was obtained from all participants after explanation of the nature and possible consequences of the study.

Eligibility was determined via demographic characteristics recording and a comprehensive ophthalmologic evaluation including measurement of uncorrected and best-corrected visual acuity, measurement of refractive error (cycloplegic refraction test for participants younger than 30-year-old, and manifest refraction test for participants of 30 years or older), slit lamp biomicroscopy examination, intraocular pressure (IOP) measurement using a Goldman applanation tonometer (Haag-Streit, Bern, Switzerland), angle evaluation using gonioscopy, dilated fundus examination, stereo disc photography (Kowa nonmyd a-D III; Kowa Optimed Inc, Aichi, Japan), visual field testing (Humphrey Visual Field Analyzer II; Carl Zeiss Meditec, Dublin, CA) using the Swedish Interactive Thresholding Algorithm (SITA) standard 24 – 2 program, and OCT scanning (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA).

For inclusion, the criteria were: (1) generally healthy individuals of age ≥ 18 years; (2) best-corrected visual acuity 20/20 or better; (3) a spherical equivalent (SE) refractive error between -5.00 diopters (D) and $+1.00$ D; (4) intraocular pressure < 21 mmHg; (5) normal and wide anterior chamber angle; (6) normal optic nerve head appearance (cup-to-disc ratio < 0.5 in either eye, with the asymmetry of ≤ 0.2 , no evidence of optic disc

hemorrhage or focal thinning of the rim); (7) reliable and normal visual field results which was defined as: mean deviation (MD) with a P value of $> 5\%$, pattern standard deviation (PSD) with a P value of $> 5\%$, no more than 3 adjacent points in the pattern deviation plot with a P value of $< 5\%$, and glaucoma hemifield test within the normal range; besides, the test should have a false-positive error, a false-negative error, and a fixation loss of less than 15%, simultaneously. The appearance of the optic disc on stereoscopic fundus photographs and visual field results were evaluated independently by two glaucoma specialists (XX and HX) who were masked to all other information about the eyes. Inconsistencies between these two doctors were decided by a senior glaucoma expert (XL). The data of the eye would not be used if the three doctors did not reach an agreement on the classification. The exclusion criteria were: (1) any known history of ocular disorders except mild or moderate refractive error; (2) history of ocular and/or brain trauma; (3) previous intraocular surgery; (4) optic media opacity; (5) medications usage that may cause IOP elevation or induce optic neuropathy; (6) neurological or systemic disorders that potentially affect visual field results and/or OCT readings; (7) unsatisfactory image acquisition; (8) inability to cooperatively complete all examinations. If both eyes of a participant met the inclusion criteria, only one randomly selected eye was enrolled.

Eligible participants underwent central cornea thickness (CCT) measurement using Ultrasonic Pachymetry (DGH-1000, Storz Inc, Louis, MO, USA) and the axial length (AL) measurement using IOLMaster (Carl Zeiss Meditec, Dublin, CA, USA).

OCT images were obtained after eyes were dilated with tropicamide 1% and phenylephrine 2.5% (Mydrin®-P, Santen Pharmaceutical Co. Ltd., Osaka, Japan) using the same OCT device by a well-trained glaucoma specialist (XX). Macular Cube 200×200 scan (200 horizontal B-scans comprising 200 A-scans per B-scan within a cube measuring $6 \times 6 \times 2$ mm centered on the fovea) and Optic Disc Cube 200×200 scan (200 horizontal B-scans comprising 200 A-scans per B-scan within a cube measuring $6 \times 6 \times 2$ mm centered on the optic disc center) were performed respectively at the same visit. Artificial tear was provided if the participants complained dryness or discomfort. Images with signal strength of less than 6 and those with visible motion or blinking artifacts and obvious segmentation failure were discarded immediately followed by repetition(s) of the scan.

The distance between the inner boundary of the GCL and the outer boundary of the IPL yields the combined thickness of the GCL and IPL (termed "GCIPL") by the ganglion cell analysis (GCA) algorithm. The GCIPL thickness were analyzed within a 14.13 mm^2 elliptical annulus area with a horizontal inner and outer radius of 0.6 and 2.4 mm, respectively; and a vertical inner and outer radius of 0.5 mm and 2.0 mm, respectively. The average, minimum, and 6 sectoral (superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal) GCIPL thickness parameters were calculated. The minimum GCIPL thickness was defined as the lowest measured value of the 1-degree intervals among all the 360 spokes. Circumpapillary RNFL thickness parameters including the average RNFL thickness and quadrant RNFL thicknesses (superior, temporal, inferior and nasal) were calculated by the Cirrus analysis algorithm.

Participants were divided into 6 groups by age with an interval of 10 years. Participants were also divided into 2 groups based on refractive error: emmetropia group (SE between -0.5D to $+1.0\text{D}$) and myopia group (SE of $<-0.5\text{D}$ and $\geq -5.0\text{D}$).

Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test and Levene test were applied to test the normality and the homogeneity of variance, respectively. Comparisons of GCIPL thickness between different gender and refractive groups were performed using independent-samples t -

test. Paired-samples t-test was used to evaluate the GCIPL thickness between the right eye and the left eye of each subject. Comparisons of the GCIPL thickness and refraction between multiple age groups were performed using one-way analysis of variance (ANOVA) with Bonferroni adjustment for pairwise comparisons. Correlations between GCIPL thickness and the following factors were analyzed using Pearson correlation coefficient: age, SE refractive error, IOP, CCT, AL, and OCT signal strength. Univariate linear regression analyses were performed to assess how age and pRNFL thickness affected GCIPL thickness. A *P* value of < 0.05 was considered statistically significant. Except where stated otherwise, the data were presented as mean ± standard deviation (SD) values.

Results

A total of 225 participants (96 males and 129 females) were enrolled. The mean age of the study population was 46.3 ± 16.5 years (range from 18 to 75 years of age). The mean (± SD) average, minimum, superotemporal, superior, superonasal, inferonasal, inferior, and inferotemporal GCIPL thickness was (84.56 ± 5.36), (81.32 ± 5.58), (83.08 ± 5.37), (85.70 ± 5.95), (87.15 ± 6.26), (85.07 ± 6.11), (82.46 ± 5.76), and (83.88 ± 5.59) µm, respectively. Variability of GCIPL thickness were assessed upon the following possible determinants:

• Gender

The mean age of 96 males and 129 females was (45.9 ± 16.7) and (47.6 ± 16.8) years, respectively. Independent-samples t-test of the age difference between genders showed no statistical significance (*t* = 0.561, *P* = 0.576). No statistically significant differences were found of average, minimum, and sectoral GCIPL thickness between genders (Table 1).

Table 1
Comparison of GCIPL Thickness between Genders (µm)

	Males	Females	<i>t</i>	<i>P</i>
Average	84.84 ± 5.21	84.33 ± 5.49	0.701	0.484
Minimum	82.04 ± 5.32	80.81 ± 5.69	1.652	0.100
Superotemporal	83.81 ± 5.18	82.53 ± 5.45	1.783	0.076
Superior	85.90 ± 5.69	85.61 ± 6.08	0.367	0.714
Superonasal	87.18 ± 6.46	86.97 ± 5.99	0.258	0.797
Inferonasal	84.91 ± 6.03	85.07 ± 6.08	-0.200	0.842
Inferior	82.58 ± 5.34	82.43 ± 6.03	0.203	0.840
Inferotemporal	84.67 ± 5.66	83.32 ± 5.42	1.828	0.069

• Laterality

Table 2 presented the comparisons of the variability between right and left eyes of all subjects, showing qualitatively similar GCIPL thickness in fellow eyes except that of the superonasal sector, where the left eyes yielded significant thicker GCIPL than the right eyes.

Table 2
Comparison of GCIPL Thickness between the Right and the Left Eyes (μm)

	OD	OS	Differences*	<i>t</i>	<i>P</i>
Average	84.40 $\pm$ 5.53	84.70 $\pm$ 5.30	-0.295 $\pm$ 2.139	-1.414	0.160
Minimum	81.25 $\pm$ 6.04	81.49 $\pm$ 5.07	-0.238 $\pm$ 4.349	-0.561	0.576
Superotemporal	83.01 $\pm$ 5.56	83.31 $\pm$ 5.05	-0.305 $\pm$ 3.010	-1.038	0.302
Superior	85.56 $\pm$ 6.12	85.95 $\pm$ 5.81	-0.390 $\pm$ 2.963	-1.350	0.180
Superonasal	86.45 $\pm$ 6.39	87.71 $\pm$ 6.04	-1.267 $\pm$ 3.256	-3.986	< 0.001
Inferonasal	85.09 $\pm$ 6.34	84.81 $\pm$ 5.81	0.276 $\pm$ 3.857	0.734	0.465
Inferior	82.50 $\pm$ 5.80	82.41 $\pm$ 5.83	0.086 $\pm$ 3.117	0.282	0.779
Inferotemporal	83.88 $\pm$ 5.69	83.83 $\pm$ 5.45	0.048 $\pm$ 3.093	0.158	0.875
OD: right eyes; OS: left eyes. *Difference: the measured value of the right eye minus the measured value of the left eye.					

• Age

Table 3 presented the GCIPL measurements and comparisons of the six age groups. Group 1 had 48 eyes of 48 subjects aged between 18–29 years (average 24.0 ± 3.5 years); Group 2 had 38 eyes of 38 subjects aged between 30–39 years (average 34.3 ± 3.0 years); Group 3 had 32 eyes of 32 subjects aged between 40–49 years (average 43.6 ± 3.0 years); Group 4 had 45 eyes of 45 subjects aged between 50–59 years (average 55.4 ± 2.3 years); Group 5 had 44 eyes of 44 subjects aged between 60–69 years (average 63.9 ± 2.5 years); and Group 6 had 18 eyes of 18 subjects aged between 70–79 years (average 72.6 ± 2.8 years). GCIPL thickness increased slowly with age in younger normal adults, after reaching its peak during 40–49 years of age, it then decreased rapidly with age. Pairwise comparisons shown significant differences in each GCIPL parameter between Group 4 and Group 5, and between Group 4 and Group 6. Given that the refractive error may have potential impacts on GCIPL thickness independent of other factors, refraction status of each age group was evaluated. The SE from Group 1 to 6 was (-2.89 ± 1.83) D, (-0.11 ± 1.67) D, (0.45 ± 0.54) D, (-0.20 ± 0.95) D, (-0.19 ± 1.03) D, and (0.70 ± 1.79) D. One-way ANOVA showed statistically significant difference ($F = 15.065$, $P < 0.001$) among the 6 groups. Further pairwise comparisons demonstrated significant differences between Group 1 and other 5 groups (all $P < 0.001$), whereas no significant difference was shown respectively between Group 2 to 6 ($P = 0.083$ – 0.969).

Table 3
Measurements (µm) and Comparisons of GCIPL Thickness between Age Groups

Group	Average	Minimum	Supero-temporal	Superior	Supero-nasal	Infero-nasal	Inferior	Infero-temporal
Measurements								
1	84.69 ± 4.56	82.13 ± 5.39	83.25 ± 4.78	86.44 ± 4.74	87.17 ± 5.46	85.19 ± 4.82	82.52 ± 4.58	83.81 ± 4.84
2	84.87 ± 5.86	82.03 ± 5.15	83.82 ± 5.43	85.84 ± 6.20	87.58 ± 7.44	85.32 ± 6.98	82.68 ± 6.24	84.21 ± 5.46
3	87.25 ± 5.94	83.31 ± 5.92	84.84 ± 5.47	88.72 ± 6.73	89.75 ± 6.92	88.16 ± 6.12	85.84 ± 6.46	86.06 ± 5.63
4	85.20 ± 3.84	81.56 ± 4.59	83.31 ± 5.42	86.53 ± 4.50	88.07 ± 3.80	86.00 ± 4.56	82.62 ± 3.98	84.47 ± 4.73
5	83.55 ± 4.97	80.34 ± 5.26	82.16 ± 5.20	83.95 ± 5.30	85.91 ± 5.60	83.77 ± 5.54	81.68 ± 5.49	83.52 ± 5.46
6	79.47 ± 6.32	76.06 ± 6.49	79.71 ± 5.68	80.59 ± 7.47	81.18 ± 6.61	78.47 ± 6.67	77.59 ± 7.20	79.18 ± 7.47
Statistics								
<i>P</i> *	< 0.001	< 0.001	0.029	< 0.001	< 0.001	< 0.001	0.003	< 0.001
1 vs 2	0.871	0.932	0.622	0.626	0.748	0.917	0.891	0.734
1 vs 3	0.029	0.331	0.187	0.076	0.057	0.023	0.008	0.069
1 vs 4	0.629	0.608	0.956	0.934	0.464	0.490	0.929	0.560
1 vs 5	0.285	0.111	0.323	0.035	0.309	0.233	0.464	0.797
1 vs 6	< 0.001	< 0.001	0.018	< 0.001	< 0.001	< 0.001	0.002	0.003
2 vs 3	0.053	0.317	0.417	0.034	0.127	0.038	0.017	0.154
2 vs 4	0.769	0.690	0.664	0.577	0.708	0.584	0.959	0.830
2 vs 5	0.244	0.156	0.157	0.130	0.204	0.220	0.410	0.565
2 vs 6	< 0.001	< 0.001	0.008	0.002	< 0.001	< 0.001	0.002	0.002
3 vs 4	0.084	0.157	0.210	0.094	0.220	0.101	0.012	0.202
3 vs 5	0.002	0.018	0.029	< 0.001	0.006	0.001	0.001	0.044
3 vs 6	< 0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
4 vs 5	0.128	0.285	0.304	0.031	0.087	0.065	0.419	0.410
4 vs 6	< 0.001	< 0.001	0.017	< 0.001	< 0.001	< 0.001	0.001	0.001

*: *P* values for general comparisons of the GCIPL parameters among all six age groups using one-way ANOVA. *P* values for pairwise comparisons between each group are presented following general comparisons.

Group	Average	Minimum	Supero-temporal	Superior	Supero-nasal	Infero-nasal	Inferior	Infero-temporal
5 vs 6	0.006	0.005	0.105	0.037	0.006	0.001	0.010	0.005
*: <i>P</i> values for general comparisons of the GCIPL parameters among all six age groups using one-way ANOVA. <i>P</i> values for pairwise comparisons between each group are presented following general comparisons.								

There was a negative correlation of GCIPL thickness and age, where a significance was shown in all analyses except that between the inferotemporal GCIPL thickness and age. Significant negative correlation of GCIPL thickness and age was found in all GCIPL parameters but the superotemporal GCIPL thickness in subjects of 40 years or older (139 eyes of 139 subjects; Table 4). The scatterplots and regression equations were presented in Fig. 1.

Table 4
Correlation and Regression Analyses between GCIPL Thickness and Age

	All subjects				Subjects of 40 years or older			
	<i>r</i>	β	95%CI for β	<i>P</i>	<i>r</i>	β	95%CI for β	<i>P</i>
Average	-0.175	-0.536	-0.935 to -0.136	0.009	-0.402	-0.710	-0.985 to -0.436	< 0.001
Minimum	-0.217	-0.641	-1.022 to -0.259	0.001	-0.339	-0.578	-0.850 to -0.307	< 0.001
Superotemporal	-0.157	-0.481	-0.883 to -0.080	0.019	-0.281	-0.495	-0.781 to 0.209	0.001
Superior	-0.215	-0.600	-0.960 to -0.240	0.001	-0.420	-0.660	-0.901 to -0.418	< 0.001
Supernasal	-0.168	-0.447	-0.794 to -0.101	0.012	-0.410	-0.657	-0.904 to -0.409	< 0.001
Inferonasal	-0.187	-0.509	-0.863 to -0.155	0.005	-0.444	-0.700	-0.939 to -0.461	< 0.001
Inferior	-0.151	-0.434	-0.809 to -0.058	0.024	-0.374	-0.609	-0.865 to -0.353	< 0.001
Inferotemporal	-0.119	-0.353	-0.742 to 0.036	0.075	-0.293	-0.489	-0.760 to -0.219	< 0.001
CI: confidence interval.								

• IOP, AL, and CCT

Mean IOP was (14.3 ± 2.5) mm Hg (ranging from 9 to 19 mm Hg). Mean AL was (23.84 ± 0.85) mm (ranging from 22.12 to 26.24 mm). Mean CCT was (554.1 ± 27.1) μ m (ranging from 497 to 628 μ m). No significant correlation was found between each GCIPL parameter with IOP, AL, and CCT (Table 5).

Table 5
Correlation between GCIPL Thickness and Intraocular Pressure, Axial Length, Central Cornea Thickness, and Refractive Error

	IOP		AL		CCT		SE	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Average	0.050	0.617	-0.096	0.339	0.065	0.516	0.107	0.285
Minimum	-0.027	0.790	-0.074	0.459	-0.046	0.645	0.039	0.696
Superotemporal	0.055	0.582	-0.078	0.435	-0.011	0.912	0.072	0.474
Superior	0.037	0.715	-0.004	0.967	0.086	0.390	0.070	0.486
Superonasal	0.062	0.536	-0.059	0.555	0.079	0.429	0.105	0.292
Inferonasal	0.015	0.880	-0.147	0.141	0.083	0.407	0.149	0.135
Inferior	0.046	0.644	-0.146	0.144	0.086	0.392	0.124	0.213
Inferotemporal	0.058	0.565	-0.098	0.327	-0.004	0.968	0.066	0.511
IOP: intraocular pressure; AL: axial length; CCT: central cornea thickness; SE: spherical equivalent refractive error.								

• Refractive error

Of all the 225 eyes enrolled in this study, the mean SE refractive error was (-0.57 ± 1.88) D, ranging from -5.00 D to $+1.00$ D. No significant correlation was found between each GCIPL parameter and SE (Table 5, last 2 columns). Participants were then divided into emmetropic group (122 eyes, mean SE of 0.60 ± 0.85 D) and myopic group (103 eyes, mean SE of -2.38 ± 1.57 D). Significant differences were only found in the inferonasal and the inferior GCIPL thickness ($t = -2.693$ and -2.293 , respectively; $P = 0.008$ and 0.024 , respectively; Table 6).

Table 6
Comparison of GCIPL Thickness between Emmetropic and Myopic Eyes (μm)

	Emmetropia	Myopia	<i>t</i>	<i>P</i>
Average	85.11 ± 6.53	83.10 ± 4.01	-1.930	0.056
Minimum	82.16 ± 5.99	80.43 ± 4.81	-1.540	0.127
Superotemporal	83.26 ± 5.86	82.08 ± 4.05	-1.205	0.231
Superior	86.26 ± 6.81	84.18 ± 4.66	-1.834	0.070
Superonasal	87.81 ± 7.52	85.83 ± 4.44	-1.671	0.980
Inferonasal	86.18 ± 7.10	83.00 ± 4.81	-2.693	0.008
Inferior	83.52 ± 6.95	80.88 ± 4.68	-2.293	0.024
Inferotemporal	83.84 ± 6.64	82.43 ± 4.43	-1.186	0.238

• RNFL thickness

The mean average, superior, temporal, inferior, and nasal RNFL thickness was (98.08 ± 9.17) μm (range: 82 to 125 μm), (123.99 ± 15.42) μm (range: 94 to 187 μm), (71.83 ± 10.76) μm (range: 55 to 102 μm), (130.17 ± 16.65) μm (range: 102 to 191 μm), and (66.25 ± 10.08) μm (range 42 to 95 μm), respectively. Significant positive correlation was found between all GCIPL thickness parameters and the average RNFL thickness (all $P < 0.001$). More correlation analyses were conducted between each GCIPL thickness parameter and the superior, temporal, inferior, and nasal RNFL thickness, respectively (Table 7). Regression analysis showed that the regression equations were statistically significant ($\beta = 0.258\text{--}0.396$, all $P < 0.001$). The scatterplots and regression equations were shown in Fig. 2.

Table 7
Correlation Analysis between GCIPL Thickness and RNFL Thickness Parameters

RNFL	Average			Superior		Temporal		Inferior		Nasal	
GCIPL	<i>r</i>	β	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Average	0.563	0.901	< 0.001	0.413	< 0.001	0.203	0.040	0.540	< 0.001	0.332	0.001
Minimum	0.423	0.693	< 0.001	0.280	0.004	0.202	0.042	0.399	< 0.001	0.251	0.011
Supero-temporal	0.508	0.889	< 0.001	0.362	< 0.001	0.223	0.024	0.463	< 0.001	0.312	0.001
Superior	0.588	0.881	< 0.001	0.447	< 0.001	0.225	0.023	0.520	< 0.001	0.373	< 0.001
Supero-nasal	0.471	0.660	< 0.001	0.341	< 0.001	0.156	0.117	0.448	< 0.001	0.302	0.002
Infero-nasal	0.461	0.654	< 0.001	0.328	0.001	0.124	0.215	0.479	< 0.001	0.264	0.007
Inferior	0.579	0.847	< 0.001	0.443	< 0.001	0.188	0.058	0.582	< 0.001	0.292	0.003
Infero-temporal	0.537	0.837	< 0.001	0.395	< 0.001	0.238	0.016	0.492	< 0.001	0.312	0.001

• OCT signal strength

The average signal strength of macular cube 200×200 scanning protocol was (7.60 ± 1.06). Based on that, the correlation between the signal strength and the GCIPL thickness was analyzed and significant positive correlations were found (Table 8).

Table 8
Correlation Analyses between GCIPL Thickness and OCT Signal Strength Using Macular Cube 200 × 200 Scanning Protocol

	GCIPL Thickness(μm)	<i>r</i>	<i>P</i>
Average	84.44 ± 5.640	0.297	<0.001
Minimum	81.57 ± 5.807	0.344	<0.001
Superotemporal	82.73 ± 0.310	0.365	<0.001
Superior	85.43 ± 5.957	0.350	<0.001
Superonasal	86.93 ± 6.414	0.319	<0.001
Inferonasal	85.33 ± 6.211	0.234	<0.001
Inferior	82.76 ± 6.324	0.395	<0.001
Inferotemporal	83.52 ± 5.871	0.341	<0.001

Discussion

In this study, we evaluated multiple determinants of macular GCIPL thickness in normal Chinese adults and demonstrated that the thinning of GCIPL thickness was associated with older age, thinner pRNFL, and weaker OCT scanning signal strength. In general, gender, laterality, refractive status (when the refractive error is between + 1D and - 5D), IOP, CCT, and AL had no significant impacts on macular GCIPL thickness.

Age is one of the most significant impact factors in determining macular GCIPL thickness. In this study, we found that the overall trend of GCIPL thickness changing with age was as follows: GCIPL thickness increased slowly with age in younger adults; after reaching the peak at 40–49 years of age, it decreased rapidly with age, which was consistent with the findings of Mwanza et al.(17) However, our previous findings in normal Chinese subjects indicated that pRNFL thickness was comparatively thicker in teenagers and reached its peak at 20–29 years of age, then gradually became thinner with age.(25) Similar results were found in studies in other Asian populations. (26, 27) These findings suggested that GCIPL and RNFL thickness changes may not necessarily be synchronized.

We found that for each additional year over 40 years of age, the average, minimum, superotemporal, superior, superonasal, inferonasal, inferior, and inferotemporal GCIPL thickness decreased by 0.229, 0.200, 0.127, 0.249, 0.273, 0.295, 0.273, and 0.173 μm , respectively. Animal experiments demonstrated that the age-related change of RGC predominately manifested as axon loss, while the RGC cell count is relatively constant.(28, 29) As the retina expands with age while the total cell counts retain, the RGC density decreases. The phenomenon of retina expansion with age was also found in human eyes, but the main difference with the animal eyes was that the number of RGC soma also declined with age in human.(30) Therefore, it is explainable that the GCIPL gets thinner with age in an OCT-based thickness evaluation, as shown in this study. It has been proven by multiple studies that the GCC or GCIPL thickness decreased with age, even though the age-related RGC loss varies in extent: Balazsi et al,(31) Repka et al,(32) Mikelberg et al,(33) Jonas et al,(34) Blanks et al,(35) Harman et al,(36) and Kerrigan-baumrind et al(37) respectively reported the annual RGC loss was between 0.07–0.61%, in studies with the sample size between 12 eyes to 72 eyes. In this study, we further approved that the age-dependent GCIPL thickness change was nonlinear with age. However, this age-related variability of the OCT measurements may not

be completely attributed to inter-subject variability in retinal neurology, which is considerably significant even in normal human eyes. When ganglion cells reduce with age, the migrant amacrine cells and other non-neuronal components may partially compensate the space which is previously predominated by ganglion cells. As such, the actual cell loss may be masqueraded and the age-RGC loss correlation may become more unpredictable. Moreover, the RGC layered in the macular region, making it more complicated to evaluate the defined pattern of region- and eccentricity-associated, age-dependent RGC loss.

When evaluating the potential causative impacts of axial length on GCIPL thickness, just as the investigations concerning its impacts on RNFL thickness, contradictory conclusions were drawn. Some studies proposed that the GCIPL and RNFL thickness were negatively correlated to axial length.(38–41) Studies with a larger sample size and/or a wider range of refractive status, generally indicated that only less than 0.5% GCIPL thickness change was attributed to per millimeter axial length change.(16–18) Such minor changes could hardly reflect any practical clinical significance. Another reason that axial length may have some impacts on the GCIPL thickness measurement, but not necessarily the actual anatomic cell counts may be ascribed to the optical effects. Since the Cirrus OCT model eye adopts a calibrated value of 24.46 mm as the default axial length setting with a fixed measuring angular distance of approximately 12°, the actual scanning area would be larger than the “standard” retinal area due to the optical magnification effect in eyes longer than 24.46 mm. As the macular ganglion cell counts drop dramatically as the eccentricity increases outward from the foveal center, average ganglion cell estimates or GCIPL thickness in these eyes may therefore be underestimated for this reason. On the contrary, in eyes shorter than the set value, the actual scanning area is smaller than the preset area where the ganglion cells are more crowded and thus a thicker GCIPL measurement may be generated falsely.

Other studies declined the direct impacts of axial length on RGC growth or apoptosis and claimed that axial length had no significant correlation with macular GCIPL thickness,(42, 43) to which our findings was consistent with. The relatively small sample size could be one possible cause. Also, our inclusive criteria for spherical equivalent refractive error were – 5.00 D and + 1.00 D. The exclusion of highly myopic eyes restricted the variability of axial length, thus minimizing the interference of magnification effects on location of the retinal area being scanned that could potentially influence the GCIPL thickness measurements. Similarly, we didn't find significant association between refractive error and GCIPL thickness. The difference of average, minimum, and most sectoral GCIPL thickness between the two refractive groups were not significantly different, except that in inferonasal and inferior sectors. Histological studies of both human and animals have found that the RGC were denser nasally than temporally, and superiorly than inferiorly, with distinct inter-subject variability, which might have indicated the discrepant anatomic distribution pattern in emmetropic and myopic eyes.(44) The thickest GCIPL was detected in the superonasal sector, in which no significant difference in emmetropic and myopic groups was found, suggesting that the density in this sector may have partially offset the difference caused by refractive error and/or axial length. This sector may have poorer performance in diagnosing glaucoma due to its least glaucomatous susceptibility.

The finding that pRNFL thickness had significant positive correlation with macular GCIPL thickness was not surprising and was consistent with previous studies.(17, 45) As the axon and soma of the ganglion cells, these two cellular components are closely related and both can be remarkably affected by glaucoma. Thus, these two parameters are both important and sensitive for early detection of glaucoma. The regression analysis showed that the mean RNFL thickness decreased by 0.901 μm for every 1 μm decrease in average GCIPL thickness. Overk et al(46) found that lesions in the axon may occur earlier than that in the soma in some neurodegenerative

diseases such as Alzheimer's disease and Parkinson's disease, indicating a 'reverse' pathogenesis pathway for the primary causative factor of glaucoma. In the pathophysiological development process of glaucoma, whether GCIPL is affected primarily and causes changes in pRNFL, or vice versa, still needs further investigations.

The stronger the OCT signal strength, the deeper retinal tissue the light achieved.(47) As the reflection of the boundaries got enhanced, the segmentation of each layer was more accurate. The signal strength of Cirrus OCT was found to be positively correlated with RNFL thickness.(48) When the signal strength reaches 7 or more, the RNFL is less likely to measure thicker as the signal strength increases. In this study, although there was significant difference between the signal strength of the Macula Cube 512 × 128 scanning protocol and that of the 200 × 200 scanning protocol, all signal strength, as our inclusion criteria indicated, was ≥ 6 . No significant difference was found in GCIPL thickness measured by the two scanning protocols, which may suggest that the GCIPL thickness measurement was stable and accurate when the signal strength is strong enough. The correlation between the signal strength of the 512 × 128 protocol and the GCIPL thickness was not as strong as that between the signal strength of the 200 × 200 protocol and the GCIPL thickness. This could be explained by the denser scan, which is more likely to generate better image quality, and the stronger signal strength of the former protocol.

There were several limitations of this study. First, it was a cross-sectional retrospective study with comparatively small sample size. Second, only ocular predictors were evaluated. Systemic predictors such as history of diabetes, cigarette smoking history, blood pressure, serum lipid levels should be taken into account. Third, there was a lack of a multivariable model synthesizing the effects of age and RNFL thickness, which were the two potential determinants found using univariable regression model. More comprehensive investigations are expected in future studies.

Conclusion

In conclusion, the GCIPL thickness measured by Cirrus OCT in normal Chinese subjects was associated with age, RNFL thickness, and scanning signal strength. No association was found between GCIPL thickness and gender, laterality, refractive status, intraocular pressure, axial length, and central corneal thickness. These should be taken into account to make comprehensive and objective clinical interpretation of GCIPL thickness in practical applications.

Abbreviations

GCIPL: ganglion cell-inner plexiform layer; **OCT**:coherence tomography; SE:spherical equivalent; IOP:intraocular pressure; AL:axial length; CCT:central cornea thickness; pRNFL:peripapillary retinal nerve fibre layer; RGC:retinal ganglion cell; ONH:optic nerve head; GCL:ganglion cell layer; GCC:ganglion cell complex; MD:mean deviation; PSD:pattern standard deviation.

Declarations

Ethics approval and consent to participate:

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Zhongshan Ophthalmic Center of Sun Yat-sen University. Written informed consent was obtained from all participants.

Consent for publication:

Consent for publication was obtained from all participants of this study.

Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

Conception and design (XL); data collection (XX, HX, JL); analysis and interpretation of data (XX, HX, KL, XG); statistical analysis (XX); literature search (XX); writing the article (XX); critical revision of the article (XX, HX, KL, XG, JL, XL). All authors reviewed and approved the final manuscript.

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Figures

Figure 1

Figure 2