Analysis of axial length, retinal nerve fiber layer, macular area and estimated retinal ganglion cell count in myopic preperimetric glaucomatous eyes: an observational study

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Abstract

BACKGROUND: The aim of the study is to evaluate the diagnostic ability of OCT parameters and retinal ganglion cells (RGCs) count in identify glaucomatous disease in myopic preperimetric eyes.

METHODS: This was a cross-sectional observational study. The study group consisted of 154 eyes: 36 healthy, 64 preperimetric (PPG), and 54 primary openangle glaucoma (POAG) eyes. Each group was divided into three subgroups based on axial length: emmetropic, myopic with axial length (AL) <25 mm, and myopic with AL>25 mm, to analyze the effect of myopia. The RGCs count was obtained using a model described later. As regard the influence of myopia on OCT parameters and RGC count, we performed Pearson’s correlation. The Area Under Receiver Operator Characteristics Curves (AUROC curves) evaluated which parameter had the best sensitivity and specificity in identifying glaucoma in myopic eyes.

RESULTS: In Pearson’s test, all Ganglion Cell Complex (GCC) thicknesses showed the weakest and less significant correlation with AL in all groups. All the AUROCs were statistically significant, and above 0.5. Inferior GCC and Global Loss Volume (GLV) showed the highest AUCs in all myopic group and the best diagnostic ability in distinguishing healthy from glaucomatous eyes. RGCcount showed good AUROC in all groups, with sensitivities of about 83% in myopic eyes, and specificity over 91% in all groups.

CONCLUSIONS: GCC is the parameter less influenced by the AL, and the inferior GCC and the GLV have the best diagnostic performance. The RGCcount has good sensitivity and specificity, so it can be used as a complementary test in the diagnosis of glaucoma in myopic preperimetric eyes.

Background

Myopia and glaucoma are two of the commonest causes of impaired vision in the world population. Myopia is projected to affect 5 billion people in the world by 2050(1), and glaucoma is a leading cause of blindness and irreversible visual impairment, affecting more than 100 million people worldwide (2,3). Myopic eyes have an increased risk of glaucoma (4). The link between myopia and glaucoma seems to be the greater deformability of the lamina cribrosa in myopic eyes. Myopic changes include longer axial lengths and vitreous chamber depths together with alterations in connective tissue which
might contribute to a higher susceptibility to glaucomatous optic disc changes (5).

With the ophthalmoscopic evaluation alone, it may be hard to tell apart myopia from glaucoma for a combination of reasons (6). The use of structural imaging or visual field testing in glaucoma is fraught with multiple potential pitfalls in myopia, such as the presence of posterior staphylomas or macular atrophy. Thus, myopic eyes may be falsely overdiagnosed with glaucoma if care is not taken to distinguish between glaucomatous and myopic pathology (7).

Recently, measurements of structural and functional tests were combined into empirical formulas for the estimation of RGCs (8–11). These estimates seem to perform better than functional and structural parameters considered separately, both for staging and monitoring the disease (9–13).

The aim of this cross-sectional observational study is to test whether Retinal Nerve Fiber Layer (RNFL) and Ganglionar Cell Complex (GCC) thicknesses are thinner in myopic PPG than emmetropic PPG and myopic healthy eyes, and whether this thickness reduction corresponds to a decrease in the estimated retinal ganglion cells (RGCs) number, so the RGCs count could be useful to identify early glaucomatous disease in myopic eyes. Another purpose of the study was to evaluate and compare the diagnostic ability of OCT parameters and RGC count in emmetropes and myopes.

**Methods**

This cross-sectional observational study was conducted at the Glaucoma Center of the Eye Clinic, Department of Surgical Sciences, University of Torino, Italy. The methods were applied in accordance to the tenets of the Declaration of Helsinki; informed consent was obtained from all subjects and the Ethics Committee (University & General Hospital San Giovanni Battista of Torino) gave approval.

To be included in the study, participants had to meet the following criteria: age between 18 and 80 years, best-corrected visual acuity (BCVA) greater than or equal to 20/30, spherical equivalent between +1.00D and -1.00 D for emmetropic subjects, and between -3.00D and -7.00D for myopic subjects, and open angle on gonioscopy. Subjects with ocular surgery, retinal or macular pathology, or systemic or neurologic conditions that could produce visual field defects, were excluded.

All subjects underwent a comprehensive ophthalmic examination consisting of: BCVA, ultrasound pachymetry, slit-lamp biomicroscopy of anterior and posterior segment, Goldmann applanation
tonometry (GAT), diurnal tonometric curve, gonioscopy, peripapillary, and macular imaging using Fourier Domain-OCT (FD-OCT RTVue-100 software version A4, 5, 0, 59; Optovue, Fremont, CA, USA), and measurement of axial length with low-coherence interferometry system (Aladdin biometer, Topcon). Standard Automated Perimetry was performed with Swedish Interactive Threshold Algorithm (SITA) Standard strategy, program 24-2 of the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Jena, Germany). Fixation losses less than or equal to 20%, false positives and false negatives less than or equal to 33% were established as the reliability criteria. The study included three groups of subjects: preperimetric glaucomatous (PPG), glaucomatous, and a control group recruited from the healthy population. The latter were required to have no family history of glaucoma, highest daily IOP less than 21 mm Hg, a normal visual field (VF) test and a normal optic nerve head (ONH) appearance. Patients affected by PPG had the highest daily IOP greater than 21 mm Hg, normal VF test, and ONH changes (cup–disc ratio alteration, disc hemorrhages, rim notching, diffused or localized RNFL defects). Primary open-angle glaucoma (POAG) was diagnosed based on the presence of highest daily IOP greater than 21 mm Hg, abnormal VF according to Hodapp-Parrish-Anderson criteria for diagnosing glaucomatous damage (14), and glaucomatous optic disc changes. Optic nerve head appearance was evaluated by slit-lamp biomicroscopy of the posterior segment using a 78-D lens. Each group was further divided into three subgroups based on axial length: emmetropic, myopic with AL<25 mm and myopic with AL>25 mm, in order to analyze the effect of mild and moderate myopia.

FD-OCT RTVue-100

The Glaucoma Protocol of FD-OCT RTVue-100 was used to acquire RNFL thickness measurements. The same operator repeated all scans three times. The RNFL thicknesses used for the analysis derived from the scan with the highest signal strength index (SSI). This scan was used to calculate RNFL thicknesses. Scans with motion artifacts and with signal strength index less than 45 were excluded.

Estimate of Retinal and Macular Ganglion Cell Count

The estimated of RGC count was obtained by applying the model developed and described in detail by Medeiros et al (9-11,15) based on the empirical formulas processed by Harwerth et al (8). We described this formula in detail in our previous article (Rolle et al.). (16)
Statistical analysis

The collection, processing and statistical analysis of the results were carried out through the Microsoft Excel 2016 worksheets and the SPSS statistical program for Windows, version 19.0, SPSS Inc, Chicago, IL. We used the analysis of variance (ANOVA) and χ² test to assess the comparability of the groups for continuous and dichotomic variables respectively.

For each of the three groups (healthy, PPG and POAG) the Pearson’s linear correlation coefficient was calculated to evaluate how the measured parameters are influenced by the AL increasing. Then, each group was further subdivided into 3 subgroups (emmetropes, myopic eyes with AL<25 mm and myopic eyes with AL>25 mm) to analyze the effects of mild and moderate axial myopia by the Mann-Whitney U test. (Figure 1)

To investigate the ability of OCT parameters and RGCount to diagnose glaucoma, we calculated areas under the receiver operating characteristic (AUROC). We compare these AUROCs between subgroups with different axial length (emmetropes, all myopic eyes, and myopes with AL<25mm and >25mm) using the method described by DeLong et al (17). The same method is used to compare the best OCT parameters and RGCs count with all the other parameters. For the calculation of AUROC and for all the comparisons between AUROCs we used a statistical software package (MedCalc v. 12.0; MedCalc Statistical software, Marakierke, Belgium).

For all statistical analysis, a p value <0.05 was considered statistically significant.

Results

The study group consisted of 154 eyes: 36 healthy, 64 PPG, and 54 POAG eyes. Demographic characteristics of the study population are illustrated in Table 1.

The ANOVA and χ² test showed that the groups are comparable for age, sex, and refraction.

Glaucomatous eyes have significantly worse VF MD and PSD than healthy and PPG eyes (P < 0.0001). RNFLavg and RGC number reduce with the progression of glaucomatous damage, as demonstrated in previous studies (16,18).

As regard the influence of myopia on OCT parameters and RGC count, we performed the Pearson’s correlation of axial length with RGC (Table 3). Almost all parameters have a moderate significant
negative correlation with axial length, except GCC thicknesses in healthy group. RGC count in healthy group shows the strongest negative correlation with AL, and all GCC thicknesses the weakest and less significant in all groups.

To better evaluate the influence of myopia, we subdivided each group in three subgroups, basing on refractive error emmetropic eyes with defect between +1.00 sf and -1.00 sf, and myopic eyes with defect between -3.00 sf and -7.00 sf, and in these latter eyes axial length superior or inferior to 25 mm. This cut-off was chosen because it is two standard deviations from the reference average of the main normative databases (19).

In Table 4.a-b-c we resumed the results of Mann-Whitney U Test between PPG and healthy subgroups. In comparisons between healthy subgroups with different axial length (Table 4.c) we can merely evaluate the influence of myopia on OCT parameters. In all comparisons the MD is not statistically significant, a sign that there is no influence of any myopic damage on the functional aspect. In all the subgroups we can observe a difference between emmetropes and myopes for both macular and papillary OCT parameters, a sign of an influence of myopia on the structural aspect.

In Table 5 we compared emmetropic PPG eyes and all myopic PPG eyes with no distinguishing about axial length, and the difference is statistically significant for all parameters.

The AUCs of MD, OCT parameters and RGCount of emmetropes, myopes with AL<25mm, myopes with AL>25mm and all myopes subjects are summarized in Tables 6.a-d and Fig. 1-4; Tables 6.a-d also shows SE, IC95%, and sensitivity and specificity of every parameters.

All the AUROCs are statistically significant, and above 0.5. Inferior GCC and Global Loss Volume (GLV) show the highest AUCs in all myopic groups and the best diagnostic ability in distinguishing healthy from glaucomatous eyes. Both GCCinf and GLV have sensibility >95% in all groups, except GLV sensitivity in all myopes’ group (92.59%). We compare AUROC of GCCinf and GLV with AUROCs of all others parameters (Table 7) using the method of DeLong (17) to test for statistical significance.

GCCinf and GLV show significant differences with MD in all comparison, with all RNFL parameters in high myopic group and in myopic group without considering AL, and only with RNFLsup if considering mild myopes group. This is probably due to the fact that the other OCT parameters also have very
good AUCs and elevated sensibility and specificity.

Table 8 shows the results of the comparisons of AUROC of MD, OCT parameters and RGCcount between groups with different axial length. All comparisons between emmetropes and myopes eyes shows statistically significant difference for all GCC parameters and GLV.

RGCcount shows very good AUC curves in all groups, with sensitivities of about 73% in emmetropic eyes, and 83% in myopic eyes, and very high specificity (over 91% in all groups, 100% in emmetropes eyes). RGCcount has the ability to identify healthy with certainty, and with good safety those with glaucoma, more in emmetropes than in myopes (but the difference of RGCcount AUROC between groups is not statistically significant).

RNFLavg and MD are used in the formula of RGCcount of Medeiros et al (9) to calculate the RGC number. We compared the diagnostic performance of both parameters with that of RGCcount (see Table 9) to assess whether the retinal ganglion cell count adds more diagnostic information than the respective parameters from which it is derived. RGCcount performs significantly better than MD in all groups, and almost the same than RNFLavg with no statistical significant differences.

Discussion

Patients with high myopia has a sixfold increased odds to develop glaucomatous disease (20), and in this case the early diagnosis is mandatory and needs tests with high sensitivity and specificity (21). The evaluation of peripapillary RNFL is used in common clinical practice to detect the presence of glaucomatous damage (22), but in high myopia its interpretation is made difficult by the frequent presence of optic nerve tilt. Shin et al (23) showed that optic disc tilt reduce RNFL diagnostic ability in detecting glaucoma, while it doesn't influence ganglion cell-inner plexiform layer (GCIPL) thickness, which is more reliable in the evaluation of glaucoma in high myopia.

In our study all the OCT parameters and RGCs count are correlated to the increase in axial length with a moderate significant negative correlation, except GCC thicknesses that seem to be the less correlated to axial length increase because they have the weakest and less significant correlation in all groups (Table 3). This is is in agreement with the results of many studies: Shoji et al (24) have shown that GCC parameters are not significantly affected by high myopia, while RNFL measurements
have a decreased ability to detect glaucoma in myopic subjects;

Considering the results of the comparisons among subgroups (Tables 4.a-b-c and 5) there are statistically significant results for almost all the parameters in comparison between healthy and PPG, both among the myopes and emmetropes. So we could support, according to the studies of Tan et al (25) and Kim et al (26), that the RNFL and GCC parameters are complementary in the evaluation of glaucomatous damage also in myopic eyes.

As regards diagnostic ability of OCT parameters, in our study all parameters has an AUROC > 0.5 (Table 6), and all curves are statistical significant, with high values of sensibility and specificity. While RNFLinf and FLV showed the best AUROCs in emmetropes, GCCinf and GLV showed the best AUROCs in all myopic group. This is in agreement with many studies that demonstrated that GCC thickness have a glaucoma detection ability as effective as that of RNFL parameters (24–30).

In the comparison between GCCinf and GLV and all other parameters, there was a statistical difference with almost all RNFL parameters, especially in high myopes (Table 7). The study of Seol et al (31) showed that inferotemporal GCIPL has a significantly better diagnostic ability than RNFL parameters, and this is in agreement with our results, and also than average GCIPL parameters, while in our study GCCinf and GLV have a better AUROC than other GCC parameters, but non statistically significant.

In Table 8 the results of the comparison of AUROC of every parameters between different subgroups are illustrated: in all the comparisons with emmetropes there is a statistical significant difference between emmetropes and myopes for GCC parameters, which show better diagnostic abilities in myopes. This means that GCC parameters are more useful to differentiate glaucomatous from healthy eyes in myopic than emmetropic eyes.

However we must take into account some limitations of GCC in the evaluation of glaucoma in myopic eyes. In the eyes in which the head of the optic nerve is deformed and therefore difficult to evaluate, we may assume that the macular region is less distorted, but this is not always true. The studies by Kim et al (32, 33) have suggested that the outline of the entire posterior pole determines the possible configuration of the optic nerve head. So, the presence of irregularities in macular region could
invalidate the evaluation of GCC in myopia. Another bias is due to the high axial length which causes a false positive GCC thinning (34). This is because a greater axial length determines a stretching of the globe with an increase in the distance between the optic nerve and the macula and consequent false thinning of macular region(35, 36). Furthermore, the presence of macular degeneration can cause GCC thinning (for retinal atrophy) or thickening (for intraretinal fluid due to myopic CNV or to macular retinoschisis) that are independent from glaucoma (37).

To our knowledge, no previous studies have reported on use of RGCs count in identify glaucoma in myopic eyes and its diagnostic ability. There are many studies about RGCount in non-myopic eyes demonstrating that a combined measure of structural and functional parameters performs better than the single OCT and perimetry parameters (13, 15). We wanted to evaluate if the diagnostic ability of the RGC was superior to those of the single parameters used in its calculation formula (MD and RNFLavg) also in myopic groups: both in mild and high myopes, AUROC of RGCount are significantly better than those of MD, and approximately similar to those of RNFLavg without statistically significant differences (Table 9). In all groups, both myopes and emmetropes, RGCount shows very good AUROC (between 0.873 in emmetropes and 0.929 in mild myopes), with sensitivity > 70% and specificity > 90%.

Based on the results of our study, RGCs count seems to be complementary to OCT parameters in the detection of glaucomatous damage in the myopia, also if GCC parameters show better diagnostic ability. Since the glaucomatous damage in the myopia is more early to be detected at macular level, it could be useful to evaluate the number of macular ganglion cells, as already done by Rolle et al (16), also in myopic subjects. This could be analysed in a further study.

The limitation of this study is that, despite of a good number of the total sample, the subdivision in different subgroups makes the number of each subgroup reduced. However, this is also found in other studies (31, 38, 39). To validate the results obtained it would be indicated to use an even larger cohort of investigation.

Another limitation is related to the fact that the sample of myopic eyes does not perfectly correspond to what we find in clinical practice, because it does not include all the eyes with perimetric alterations
(enlarged blind spot, general reduction of sensitivity and superotemporal peripheral defects), which also are very frequent in myopic eyes.

A strength is represented by the use of preperimetric eyes, since comparing only eyes diagnosed with both functionally and structurally established glaucoma with healthy would lead to overestimate the performance of the test, as reported by Medeiros et al (40).

Conclusions
In conclusion, in the OCT analysis of myopic eyes RNFL is the parameter most influenced by the axial length, while the GCC, in particular the inferior, and the GLV are the two OCT parameters with better diagnostic performance. The RGCcount appears to have good sensitivity and specificity, but not higher than the OCT parameters, so it can be used as a complementary test in the diagnosis of glaucoma in myopic eyes.

Identifying the presence of glaucoma in a myopic eye is one of the current diagnostic challenges in ophthalmology, and we must interpret all the instrumental data considering the influence of myopia. Current OCTs analyze the thicknesses of retinal nerve fibers and ganglion cells using a normative database that includes emmetropic subjects. Our study agrees with other works affirming that the OCT parameters are affected, although to varying degrees, by the axial length. Therefore to increase the reliability of the OCT in the diagnosis it would be appropriate to insert myopic eyes in the normative databases of the instruments and develop algorithms that take into account the axial length to analyze the thicknesses detected with OCT.

Abbreviations
AL
Axial Length
BVCA
Best Corrected Visual Acuity
FD
Fourier-Domain
FLV
Focal Loss Volume
GCC
Ganglion Cell Complex
GLV
Global Loss Volume
IOP
Intra-ocular Pressure
MD
Mean Deviation
OCT
Optical Coherence Tomography
ONH
Optic Nerve Head
POAG
Primary Open Angle Glaucoma
PPG
Preperimetric Glaucoma
PSD
Pattern Standard Deviation
RGC
Retinal Ganglion Cell
RNFL
Retinal Nerve Fiber Layer
VF
Visual Field

Declarations
ETHICS APPROVAL AND CONSENT TO PARTECIPATE
This study followed the tenets of the Declaration of Helsinki and approved by the ethics committee of the University & General Hospital San Giovanni Battista of Torino. Informed written consent was obtained from all participants.

COMPETING INTERESTING
The authors declare that they have no competing interests

FUNDING
This study was not supported by any research grants.

AVAILABILITY OF DATA AND MATERIALS
The data have not been placed in any online data storage. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

AUTHORS’ CONTRIBUTION

Study concept and design (TR, BB, AM); collection, management, analysis, and interpretation of data (BB, AM); preparation, review, or approval of the manuscript (TR, BB, AM, LD). All authors read and approved the final manuscript.

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Tables
TABLE 1. Comparison of the Demographic and Clinical Characteristics of Healthy Eyes, PPG, and POAG Eyes.

| PARAMETERS                | HEALTHY      | PPG          | POAG         | P   |
|---------------------------|--------------|--------------|--------------|-----|
| EYES (n)                  | 36           | 64           | 54           |     |
| AGE (y)                   | 55.51 (7.72) | 56.00 (7.28) | 59.93 (7.28) |     |
| SEX (M/F)                 | 16/20        | 15/39        | 22/32        |     |
| REFRACTION (D)            | -2.53 (2.45) | -2.49 (2.65) | -3.24 (2.74) |     |
| AXIAL LENGTH (mm)         | 24.18 (1.16) | 24.28 (2.19) | 24.99 (2.75) |     |
| MD (dB)                   | -0.48 (0.83) | -0.59 (1.64) | -6.50 (6.74) |     |
| PSD (dB)                  | 1.63 (0.37)  | 1.75 (0.96)  | 6.30 (3.63)  |     |
| RNFLavg (µ)               | 108.22 (10.90) | 93.70 (9.95) | 80.24 (13.2) |     |
| GCCavg (µ)                | 97.11 (6.46) | 85.52 (7.32) | 75.19 (10.95) |     |
| estimated total RGC count | 1140520.81 (138535.47) | 958579.68 (150472.40) | 616463.06 (226325.70) |     |

The parameters are expressed as mean and SD; MD: Mean deviation of SAP; PSD: pattern standard deviation of SAP. RNFL: Retinal Nerve Fiber Layer; GCC: Ganglion Cell Complex; RGC: Retinal Ganglion Cell.

* P-value for ANOVA, significant for p<0.05
† P-value for χ² test, significant for p<0.05
TABLE 2. Comparison of the Demographic and Clinical Characteristics of Emmetropic Eyes, Myopes with AL<25mm and AL>25mm.

| PARAMETERS                  | EMMETROPS | MYOPES AL<25mm | MYOPES AL>25 mm |
|----------------------------|-----------|----------------|-----------------|
| EYES (n)                   | 50        | 51             | 53              |
| AGE (y)                    | 58.92 (8.67) | 57.94 (10.76) | 57.89 (11.36)  |
| SEX (M/F)                  | 18/32     | 16/35          | 19/34           |
| REFRACTION (D)             | 0.64 (0.34) | -3.62 (0.43)  | -5.24 (1.10)   |
| AXIAL LENGTH (mm)          | 22.82 (0.80) | 24.41 (0.61)  | 26.23 (1.30)   |
| MD (dB)                    | -2.16 (4.43) | -2.18 (5.37)  | -3.50 (5.30)   |
| PSD (dB)                   | 2.77 (2.23)  | 3.39 (3.42)    | 3.76 (3.67)    |
| RNFLavg (µ)                | 96.43 (14.06)| 95.23 (16.66) | 86.02 (13.58)  |
| GCCavg (µ)                 | 87.63 (7.70) | 85.12 (14.50) | 81.59 (11.87)  |
| estimated total RGC count  | 941639.43 (259924.16) | 918347.12 (279783.75) | 786566.29 (260723.37) |

The parameters are expressed as mean and SD; MD: Mean deviation of SAP; PSD: pattern standard deviation of SAP. RNFL: Retinal Nerve Fiber Layer; GCC: Ganglion Cell Complex; RGC: Retinal Ganglion Cell.

* P-values for ANOVA, significant for p<0.05

† P-values for χ² test, significant for p<0.05


TABLE 3. Pearson’s correlation between OCT parameters and RGC count and axial length

| PARAMETERS       | Healthy          | PPG              | POAG             |
|------------------|------------------|------------------|------------------|
|                  | R (p)            | R (p)            | R (p)            |
| MD (dB)          | -0.28 (0.05)     | -0.07 (0.56)     | -0.34 (0.01)     |
| RNFLavg (µm)     | -0.46 (0.002)    | -0.33 (0.003)    | -0.3 (0.01)      |
| RNFLsup (µm)     | -0.31 (0.03)     | -0.28 (0.01)     | -0.3 (0.03)      |
| RNFLinf (µm)     | -0.55 (<.001)    | -0.31 (0.007)    | -0.3 (0.01)      |
| GCCavg (µm)      | 0.07 (0.3)       | -0.29 (0.01)     | -0.15 (0.1)      |
| GCCsup (µm)      | 0.1 (0.3)        | -0.23 (0.03)     | -0.04 (0.4)      |
| GCCinf (µm)      | 0.045 (0.4)      | -0.31 (0.006)    | -0.24 (0.04)     |
| FLV %            | 0.44 (0.004)     | 0.43 (<.001)     | 0.57 (<.001)     |
| GLV %            | 0.22 (0.1)       | 0.48 (<.001)     | 0.26 (0.03)      |
| RGCcount (n)     | -0.58 (<.001)    | -0.3 (<.001)     | -0.32 (0.007)    |

P-values significant for p < 0.05
The parameters are expressed as mean and SD. There is no difference between emmetropic and mild myopic PPG, while all the parameters analyzed are statistically significant in comparison between emmetropes and high myopic PPG, and between mild and high myopic PPG. P-values significant for \( p < 0.05 \).
Table 4b. Mann-Whitney U Test between PPG and healthy eyes with the same axial length.

| PARAMETER | PPG emmetropic (N=22) | PPG with AL<25 mm (N=21) | PPG with AL>25mm (N=21) | Healthy emmetropic (N=13) | Healthy with AL<25 mm (N=12) | Healthy with AL>25 mm (N=11) |
|-----------|------------------------|--------------------------|--------------------------|---------------------------|-----------------------------|-----------------------------|
| MD (dB)   | -0.98 (1.52)           | -0.94 (1.89)             | 0.18 (1.26)              | -0.12 (0.85)              | -0.64 (0.79)                | -0.73 (0.76)                |
| RNFL avg (µm) | 97.17 (10.82)         | 88.68 (9.07)             | 95.09 (8.05)             | 109.76 (9.79)             | 114.54 (10.61)              | 100.15 (7.59)               |
| RNFL sup (µm) | 98.01 (11.01)         | 90.30 (12.07)            | 93.52 (8.78)             | 106.45 (9.32)             | 113.45 (13.76)              | 101.04 (10.04)              |
| RNFL inf (µm) | 96.31 (11.84)         | 87.06 (11.22)            | 96.66 (10.66)            | 113.08 (11.48)            | 115.62 (9.26)               | 99.30 (7.78)                |
| GCC avg (µm) | 88.20 (6.68)          | 81.52 (8.64)             | 86.73 (4.60)             | 92.70 (4.37)              | 102.24 (6.68)               | 96.75 (4.12)                |
| GCC sup (µm) | 88.99 (7.31)          | 82.82 (8.16)             | 87.86 (5.11)             | 91.66 (4.96)              | 100.96 (7.20)               | 96.86 (5.37)                |
| GCC inf (µm) | 87.40 (7.04)          | 80.22 (9.91)             | 85.66 (5.02)             | 93.74 (4.05)              | 103.60 (6.56)               | 96.62 (3.73)                |
| FLV %      | 1.68 (2.22)           | 4.50 (4.67)              | 2.41 (2.74)              | 0.20 (0.22)               | 0.34 (0.46)                 | 1.00 (1.09)                 |
| GLV %      | 9.59 (5.71)           | 18.07 (7.16)             | 12.29 (4.68)             | 4.69 (2.76)               | 1.57 (1.50)                 | 4.99 (2.21)                 |
| RGC count (n) | 1002394.31 (189401.24) | 1183055.86 (125256.44)   | 986664.15 (91736.86)     | 884594.19 (128656.99)     | 1191809.55 (129243.34)      | 1034300.79 (109779.01)      |

The parameters are expressed as mean and SD. RNFLavg and RGCs count are significant in all comparisons, while GCCavg is not significant in the comparison between PPG and healthy emmetropes. P-values significant for $p<0.05$. 
Table 4.c P-value for Mann-Whitney U Test between healthy eyes with different axial length

| PARAMETERS | Healthy emmetropic (N=13) | Healthy with AL<25mm (N=12) | Healthy with AL>25 mm (N=11) | Healthy emmetropic vs healthy with AL<25mm | Healthy emmetropic vs healthy with AL>25mm | Healthy with AL<25mm vs healthy with AL>25mm |
|------------|---------------------------|-----------------------------|-------------------------------|-------------------------------------------|------------------------------------------|--------------------------------------------|
| MD (dB)    | -0.12 (0.85)              | -0.64 (0.79)                | -0.73 (0.76)                  | 0.11                                      | 0.12                                      | 0.83                                       |
| RNFL avg (µm) | 109.76 (9.79)          | 114.54 (10.61)              | 100.15 (7.59)                 | 0.31                                      | **0.04**                                  | **0.003**                                  |
| RNFL sup (µm) | 106.45 (9.32)          | 113.45 (13.76)              | 101.04 (10.04)                | 0.18                                      | 0.12                                      | **0.003**                                  |
| RNFL inf (µm) | 113.08 (11.48)         | 115.62 (9.26)               | 99.30 (7.78)                  | 0.81                                      | **0.01**                                  | **0.02**                                   |
| GCC avg (µm) | 92.70 (4.37)            | 102.24 (6.68)               | 96.75 (4.12)                  | <.001                                     | 0.05                                      | **0.03**                                   |
| GCC sup (µm) | 91.66 (4.96)            | 100.96 (7.20)               | 96.86 (5.37)                  | **0.004**                                 | 0.06                                      | 0.13                                       |
| GCC inf (µm) | 93.74 (4.05)            | 103.60 (6.56)               | 96.62 (3.73)                  | <.001                                     | 0.09                                      | **0.005**                                  |
| FLV %     | 0.20 (0.22)              | 0.34 (0.46)                 | 1.00 (1.09)                   | 0.60                                      | **0.04**                                  | **0.05**                                   |
| GLV %     | 4.69 (2.76)              | 1.57 (1.50)                 | 4.99 (2.21)                   | **0.005**                                 | 0.68                                      | <.001                                      |
| RGC count (n) | 1183055.86 (125256.44) | 1191809.55 (129243.34)      | 1034300.79 (109779.01)        | 0.76                                      | **0.01**                                  | **0.007**                                  |

The parameters are expressed as mean and SD. P-values significant for p<0.05.
### TABLE 5 Mann–Whitney U Test between subgroups

| PARAMETERS | Emmetropic PPG | Myopic* PPG | Healthy myopes† | Non-highly myopic‡ | Highly myopic§ | Emmetropic PPG vs Myopic* PPG |
|------------|----------------|-------------|-----------------|--------------------|----------------|-------------------------------|
| MD (dB)    | -0.98 (1.52)   | -0.38 (1.69)| -0.69 (0.76)    | -2.12 (6.09)       | -3.58 (5.16)  | 0.04                          |
| RNFL avg (µm) | 97.17 (10.82) | 91.89 (9.07)| 107.66 (11.68)  | 94.69 (13.23)      | 86.46 (13.87) | 0.03                          |
| RNFL sup (µm) | 98.01 (11.01) | 91.91 (10.55)| 107.51 (13.44)  | 95.05 (13.26)      | 88.15 (15.30) | 0.02                          |
| RNFL inf (µm) | 96.31 (11.84) | 91.86 (11.85)| 107.81 (14.57)  | 94.31 (14.88)      | 84.78 (11.78) | 0.17                          |
| GCC avg (µm) | 88.20 (6.68)  | 84.12 (7.32)| 99.61 (6.16)    | 84.77 (8.88)       | 81.61 (11.78) | 0.01                          |
| GCC sup (µm) | 88.99 (7.31)  | 85.34 (7.19)| 99.00 (6.59)    | 86.15 (8.62)       | 83.43 (11.79) | 0.02                          |
| GCC inf (µm) | 87.40 (7.04)  | 82.94 (8.24)| 100.26 (6.37)   | 83.41 (10.58)      | 79.78 (13.14) | 0.03                          |
| FLV %       | 1.68 (2.22)    | 3.46 (3.93)| 0.66 (0.87)     | 4.22 (3.74)        | 5.96 (5.39)   | 0.002                         |
| GLV %       | 9.59 (5.71)    | 15.18 (6.65)| 3.21 (2.53)     | 15.19 (7.85)       | 18.39 (10.28) | 0.008                         |
| RGC count (n) | 1002394.31 (189401.24) | 935629.17 (121851.31) | 1116479.27 (142484.24) | 910940.59 (226819.93) | 784036.59 (253833.31) | <.001                         |

The parameters are expressed as mean and SD. P-values significant for p<0.05.

* Myopes with preperimetric glaucoma, without distinction for axial length

† Healthy myopic eyes with no distinction for axial length

‡ Healthy and PPG eyes with AL<25mm

§ Healthy and PPG eyes with AL>25mm

### TABLE 6.a ROC curves in emmetropic eyes

| AUC (CI95%)   | CUT OFF | p       | %SENS (95%CI) |
|---------------|---------|---------|---------------|
| MD (dB)       | 0.807 (0.670 to 0.987) | -0.35    | <.001         | 83.78 (68.0 - 93.8) | 6.1% |
TABLE 6.b ROC curves in all myopic eyes

|        | Value          | Cut-off | Sensibility | Specificity | P-value |
|--------|----------------|---------|-------------|-------------|---------|
| MD (dB) | 0.636 (0.536 to 0.728) | -2.51   | 0.008       | 50.62 (39.3 - 61.9) | 8p      |
| RNFL avg (µm) | 0.899 (0.824 to 0.949) | 95.56   | <.001       | 80.25 (69.9 - 88.3) | 8p      |
| RNFL sup (µm) | 0.87 (0.789 to 0.928) | 90.48   | <.001       | 66.67 (55.3 - 76.8) | 8p      |
| RNFL inf (µm) | 0.885 (0.808 to 0.939) | 97.07   | <.001       | 75.31 (64.5 - 84.2) | 8p      |
| GCC avg (µm) | 0.981 (0.933 to 0.998) | 93.19   | <.001       | 97.53 (91.4 - 99.7) | 8p      |
| GCC sup (µm) | 0.953 (0.893 to 0.985) | 91.01   | <.001       | 90.12 (81.5 - 95.6) | 8p      |
| GCC inf (µm) | 0.987 (0.942 to 0.999) | 92.27   | <.001       | 97.53 (91.4 - 99.7) | 8p      |
| FLV % | 0.917 (0.846 to 0.962) | 0.806   | <.001       | 90.12 (81.5 - 95.6) | 8p      |
| GLV % | 0.987 (0.941 to 0.999) | 8.658   | <.001       | 92.59 (84.6 - 97.2) | 8p      |
| RGC count (n) | 0.895 (0.820 to 0.947) | 935606.84 | <.001       | 70.37 (59.2 - 80.0) | 8p      |

*Area under receiver operating characteristic curve values with 95% CIs, cut off, sensibility and*
specificity and their CI95% describing glaucomatous diagnostic capabilities of OCT parameters and 
RGC count in emmetropic (6.a) and all myopic eyes (6.b). P-values significant for p<0.05.

**TABLE 6.c ROC curves in myopic eyes with AL<25 mm**

| Parameter         | AUC (CI95%)          | Cut off | p    | %SENS (95%CI)      |
|-------------------|----------------------|---------|------|--------------------|
| MD (dB)           | 0.528 (0.383 to 0.669) | -2.78   | 0.72 | 38.46 (23.4 - 55.4) |
| RNFL avg (µm)     | 0.951 (0.851 to 0.992) | 99.15   | <.001| 82.05 (66.5 - 92.5) |
| RNFL sup (µm)     | 0.912 (0.799 to 0.973) | 108.33  | <.001| 94.87 (82.7 - 99.4) |
| RNFL inf (µm)     | 0.949 (0.848 to 0.991) | 102.09  | <.001| 84.62 (69.5 - 94.1) |
| GCC avg (µm)      | 0.995 (0.920 to 1.000) | 93.19   | <.001| 97.44 (86.5 - 99.9) |
| GCC sup (µm)      | 0.951 (0.851 to 0.992) | 93.12   | <.001| 89.74 (75.8 - 97.1) |
| GCC inf (µm)      | 0.998 (0.926 to 1.000) | 92.27   | <.001| 97.44 (86.5 - 99.9) |
| FLV %             | 0.949 (0.848 to 0.991) | 0.799   | <.001| 89.74 (75.8 - 97.1) |
| GLV %             | 0.996 (0.922 to 1.000) | 4.001   | <.001| 97.44 (86.5 - 99.9) |
| RGC count (n)     | 0.929 (0.822 to 0.982) | 1054836.71 | <.001| 84.62 (69.5 - 94.1) |

**TABLE 6.d ROC curves in myopic eyes with AL>25 mm**

| Parameter         | AUC (CI95%)          | Cut off | p    | %SENS (95%CI)      |
|-------------------|----------------------|---------|------|--------------------|
| MD (dB)           | 0.733 (0.593 to 0.845) | -2.09   | <.001| 64.29 (48.0 - 78.4) |
| RNFL avg (µm)     | 0.883 (0.765 to 0.955) | 87.37   | <.001| 66.67 (50.5 - 80.4) |
| RNFL sup (µm)     | 0.859 (0.736 to 0.939) | 90.48   | <.001| 78.57 (63.2 - 89.7) |
| RNFL inf (µm)     | 0.872 (0.752 to 0.948) | 86.29   | <.001| 71.43 (55.4 - 84.3) |
| GCC avg (µm)      | 0.974 (0.888 to 0.998) | 89.89   | <.001| 92.86 (80.5 - 98.5) |

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| Parameter          | Mean (95% CI) | Area under ROC curve | 95% CI | P-value | Note |
|-------------------|---------------|----------------------|-------|---------|------|
| GCC sup (µm)      | 0.963 (0.872 to 0.996) | 89.07 | <.001 | 88.1 (74.4 - 96.0) | 1 |
| GCC inf (µm)      | **0.976** (0.891 to 0.999) | 89.52 | <.001 | 95.24 (83.8 - 99.4) | 1 |
| FLV %             | 0.9 (0.787 to 0.966) | 3.408 | <.001 | 71.43 (55.4 - 84.3) | 1 |
| GLV %             | **0.998** (0.929 to 1.000) | 8.658 | <.001 | 97.62 (87.4 - 99.9) | 1 |
| RGC count (n)     | 0.905 (0.792 to 0.968) | 933043.19 | <.001 | 83.33 (68.6 - 93.0) | 9 |

*Area under receiver operating characteristic curve values with 95% CIs, cut off, sensibility and specificity and their CI95% describing glaucomatous diagnostic capabilities of OCT parameters and RGC count in myopes with AL<25 mm eyes (6.c) and myopes with AL>25 mm eyes (6.d). P-values significant for \( p < 0.05 \).*
|                  | GCCinf | GLV | GCCinf | GLV | GCCinf |
|------------------|--------|-----|--------|-----|--------|
|                  | Differenc e between areas (SE) | p | Differenc e between areas (SE) | p | Differenc e between areas (SE) | p |
| **MD (dB)**      | 0.5 (0.08) | *<.001* | 0.5 (0.08) | *<.001* | 0.2 (0.07) | *<.001* | 0.3 (0.07) | *<.001* | 0.351 (0.05) | *<.01* |
| **RNFL avg (µm)**| 0.05 (0.03) | 0.1 | 0.05 (0.03) | 0.09 | 0.09 (0.04) | *0.03* | 0.1 (0.05) | *0.01* | 0.09 (0.03) | *0.01* |
| **RNFL sup (µm)**| 0.09 (0.05) | *0.05* | 0.08 (0.04) | *0.04* | 0.11 (0.05) | *0.02* | 0.14 (0.05) | *0.005* | 0.1 (0.03) | *<.01* |
| **RNFL inf (µm)**| 0.05 (0.03) | 0.08 | 0.05 (0.03) | 0.07 | 0.1 (0.04) | *0.01* | 0.13 (0.01) | *0.007* | 0.1 (0.03) | *0.01* |
| **GCC avg (µm)** | 0.003 (0.007) | 0.6 | 0.001 (0.007) | 0.9 | 0.002 (0.003) | 0.4 | 0.02 (0.02) | 0.2 | 0.006 (0.005) | 0 |
| **GCC sup (µm)** | 0.05 (0.03) | 0.1 | 0.05 (0.03) | 0.1 | 0.01 (0.01) | 0.3 | 0.03 (0.02) | 0.1 | 0.03 (0.02) | 0.0 |
| **GCC inf (µm)** | /// | /// | 0.002 (0.004) | 0.6 | /// | /// | 0.02 (0.02) | 0.3 | /// | /// |
| **FLV %**        | 0.05 (0.03) | 0.09 | 0.05 (0.03) | 0.1 | 0.08 (0.05) | 0.1 | 0.1 (0.05) | *0.03* | 0.07 (0.03) | 0.0 |
| **GLV %**        | 0.002 (0.004) | 0.6 | /// | /// | 0.02 (0.02) | 0.2 | /// | /// | 0.0005 (0.009) | 0.0 |
| **RGC count (n)** | 0.07 (0.04) | 0.07 | 0.07 (0.04) | 0.07 | 0.07 (0.05) | 0.1 | 0.09 (0.04) | *0.03* | 0.09 (0.03) | *0.01* |

*P-values significant for p<0.05*
### TABLE 8 Comparison of AUROCs of all OCT parameters between subgroups with different axial length.

|                          | Emmetropes vs Myopes | Emmetropes vs Myopes with AL<25mm | Emmetropes vs Myopes with AL>25mm | Myopes vs Myopes |
|--------------------------|----------------------|-----------------------------------|-----------------------------------|-----------------|
| **Difference between areas (SE)** | **p** | **Difference between areas (SE)** | **p** | **Difference between areas (SE)** | **p** | **Difference between areas (SE)** |
| **MD (dB)**              | 0.171 (0.0814)       | 0.04                              | 0.279 (0.103)                     | 0.006           | 0.074 (0.095) | 0.44 | -0.205 (0.101) |
| **RNFL avg (µm)**       | -0.022 (0.0762)      | 0.72                              | -0.074 (0.0702)                   | 0.22            | -0.006 (0.0797) | 0.12 | 0.068 (0.0551) |
| **RNFL sup (µm)**       | -0.072 (0.0635)      | 0.34                              | -0.114 (0.0802)                   | 0.15            | -0.061 (0.0841) | 0.47 | 0.053 (0.0664) |
| **RNFL inf (µm)**       | -0.005 (0.0737)      | 0.94                              | -0.069 (0.0606)                   | 0.25            | 0.008 (0.0721) | 0.91 | 0.077 (0.0558) |
| **GCC avg (µm)**        | -0.233 (0.0737)      | **0.002**                          | -0.247 (0.073)                    | <.001           | -0.226 (0.076) | 0.003 | 0.021 (0.0231) |
| **GCC sup (µm)**        | -0.28 (0.0845)       | **0.01**                           | -0.278 (0.087)                    | **0.001**       | -0.29 (0.0859) | <.001 | 0.077 (0.0378) |
| **GCC inf (µm)**        | -0.186 (0.0632)      | **0.003**                          | -0.197 (0.0626)                   | **0.002**       | -0.175 (0.0662) | **0.008** | 0.022 (0.0221) |
| **FLV %**               | -0.02 (0.0545)       | 0.71                              | -0.052 (0.0554)                   | 0.34            | -0.003 (0.0635) | 0.96 | 0.049 (0.0537) |
| **GLV %**               | -0.169 (0.0658)      | **0.01**                           | -0.178 (0.0655)                   | **0.007**       | -0.18 (0.0654) | **0.006** | -0.002 (0.00599) |
| **RGC count (n)**       | -0.022 (0.0588)      | 0.71                              | -0.056 (0.0617)                   | 0.36            | -0.032 (0.0648) | 0.62 | 0.024 (0.0568) |

*P-values significant for p<0.05*
### TABLE 9 Comparison of AUROCs between RGCcount and OCT parameters, in all myopes groups.

|                | EMMETROPES | MYOPES WITH AL<25mm | MYOPES WITH AL>25mm | ALL   |
|----------------|------------|---------------------|---------------------|-------|
|                | RGCcount   | p                   |                     |       |
| Difference      | p          | Difference          |                     |       |
| between areas   | p          | between areas       |                     |       |
| (SE)            | p          | (SE)                |                     |       |
| MD (dB)         | 0.0665     | 0.16                | 0.402               | <.001 |
|                 | (0.0476)   | (0.0792)            | (0.072)             | 0.008 |
| RNFL avg (µm)   | 0.00416    | 0.93                | 0.0214              | 0.55  |
|                 | (0.0463)   | (0.354)             | (0.354)             | 0.66  |
| RNFL sup (µm)   | 0.0716     | 0.2                 | 0.0171              | 0.7   |
|                 | (0.0558)   | (0.0414)            | (0.0414)            | 0.39  |
| RNFL inf (µm)   | 0.0107     | 0.83                | 0.0192              | 0.53  |
|                 | (0.0496)   | (0.309)             | (0.309)             | 0.54  |
| GCC avg (µm)    | 0.125      | 0.08                | 0.0652              | 0.08  |
|                 | (0.0704)   | (0.0375)            | (0.0375)            | 0.42  |
| GCC sup (µm)    | 0.197      | 0.02                | 0.0214              | 0.64  |
|                 | (0.0821)   | (0.0451)            | (0.0451)            | 0.23  |
| GCC inf (µm)    | 0.0748     | 0.23                | 0.0684              | 0.73  |
|                 | (0.0618)   | (0.0382)            | (0.0382)            | 0.13  |
| FLV %           | 0.0278     | 0.7                 | 0.0192              | 0.7   |
|                 | (0.0731)   | (0.0502)            | (0.0502)            | 0.94  |
| GLV %           | 0.0603     | 0.39                | 0.0662              | 0.07  |
|                 | (0.0705)   | (0.0369)            | (0.0369)            | 0.03  |

*P-values significant for p<0.05*

**Figures**
Figure 1

Graphical representation of the subdivision of the study sample into subgroups
AUROC of RNFLavg, GCCinf, GLV, RGCcount and MD in emmetropic eyes (Fig. 2), myopes with AL<25 mm (Fig 3), myopes with AL>25mm (Fig. 4) and all myopic eyes with no distinction in axial length (Fig 5)
AUROC of RNFLavg, GCCinf, GLV, RGCount and MD in emmetropic eyes (Fig. 2), myopes with AL<25 mm (Fig 3), myopes with AL>25mm (Fig. 4) and all myopic eyes with no distinction in axial length (Fig 5)
AUROC of RNFLavg, GCCinf, GLV, RGCount and MD in emmetropic eyes (Fig. 2), myopes with AL<25 mm (Fig 3), myopes with AL>25mm (Fig. 4) and all myopic eyes with no distinction in axial length (Fig 5)
AUROC of RNFLavg, GCCinf, GLV, RGCount and MD in emmetropic eyes (Fig. 2), myopes with AL<25 mm (Fig 3), myopes with AL>25mm (Fig. 4) and all myopic eyes with no distinction in axial length (Fig 5)