COMPARISON OF CUP-TO-DISC RATIOS AS MEASURED USING OCULAR COHERENCE TOMOGRAPHY AND STEREOSCOPIC FUNDUS PHOTOGRAPHY

by

Mark Debano Jr. and Matthew Tholl

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Has been approved

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APPROVED:

____________[redacted]______________, Brian McDowell OD

ACCEPTED:

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Avesh Raghunadan OD, PhD, FAAO

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ABSTRACT

Background: The purpose of this research project is to compare cup-to-disc (C/D) ratios as measured with the Cirrus (Zeiss) ocular coherence tomography (OCT) and stereoscopic fundus photography of the same subject. *Methods:* At the University Eye Center in Big Rapids, MI, subjects will have each eye photographed stereoscopically using a fundus camera. Subjects will have each of their eyes analyzed using the OCT and the report, containing the instruments optic nerve head measurements, will be obtained. The subjective measurements will then be compared to the calculated values as measured with the OCT. The subject activities will be limited to aforementioned and are expected to take approximately five minutes. *Results:* Interclass correlation coefficients for the group of average C/Ds and vertical C/Ds shows good agreement with the clinician's average assessment (CAA) However, when the C/Ds are divided into subgroups based on size, there appears to be little agreement. The mean of the clinician's ICC also appears to be low for subgroups. *Conclusions:* Inter-observer variability can have an effect on the clinical care of a patient so the widespread use of instrumentation when assessing the C/D ratio can be useful. This study demonstrates that inconsistency exists when relying solely on objective measurement techniques, such as the Cirrus HD-OCT, compared to the fundoscopic assessment of the C/D.

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Introduction

Thorough evaluation of the cup-to-disc (C/D) ratio is an important clinical assessment in determining the progression and proper diagnosis of ocular pathology, particularly glaucoma. The C/D ratio is represented as a fraction, comparing the diameter of the cup to the diameter of the optic disc. The comparison of the two measurements is important since the size of the disc, not the cupping alone, is critical for accurate assessment of the optic nerve head (ONH). Vertical enlargement of the C/D ratio (or alternatively, loss of inferior and superior neuroretinal rim tissue) is a well-documented occurrence in many forms of glaucoma. In addition to the C/D ratio, the integrity of the neuroretinal rim tissue is assessed for color, appearance, and the presence of other pathology.

The optical coherence tomographer (OCT) is an important clinical tool that can be used to assess the C/D ratio of a patient and examine optic nerve integrity. This scanning laser technology is capable of producing a high-resolution topographical and cross-sectional image. The Cirrus HD-OCT's optic disc cube 200X200 protocol used in this study does this by capturing a 6x6mm cube of data in 1.5 seconds using a laser that performs 200 A-scans and 200 B-scans (a total of 40,000 data points).

Photography of the ONH is important in management and monitoring of change over time in a glaucoma patient or a patient with optic nerve pathology. Stereophotographs traditionally were the gold standard for documentation of the optic nerve. Retinal cameras frequently come equipped with stereoscopic photograph capabilities, which can help the examiner more accurately inspect the ONH and determine the C/D ratio. These photographs can be printed and accompany the file of the patient to ensure proper care and management.

Despite the frequent utilization of stereophotographs and other technologies, like the OCT, clinicians still prefer to assess the ONH by taking a first-hand, ophthalmoscopic view using high-powered fundus lenses (e.g., 90D, 78D, 60D).

When examining the ONH, there are inherent variables to consider. For example the compensation factor for high plus lenses used when measuring the optic disc, anatomical variations, and inter-observer variability when co-managing a patient. Inter-observer variability has been determined to be more of a factor than intra-observer variability and needs to be considered when co-managing patients (Spalding et al, 2000).

Comparing the methods of ONH evaluation allows for consistency in the care of a patient. The Cirrus HD-OCT (Zeiss) is a common OCT currently used in many optometry and ophthalmology practices. This study aims to compare the agreement between this particular OCT's assessment of the average C/D and the vertical C/D, and the optometric clinician's assessment of these parameters.

Methods

A total of 86 data points were collected from 43 subjects at the University Eye Center affiliated with the Michigan College of Optometry. Anatomical variations between subjects were minimized in the test population by disqualifying potential subjects that answered in a positive manner with the screening questions. After this initial screening, some data points were excluded from the study that included poor reliability from the OCT scan or from the poor quality of the stereoscopic photo. All participants have had no prior ocular diagnoses that involve the optic nerve and were considered to have good ocular health.

Subjects selected for this study were imaged by the Cirrus HD-OCT in one day. Subject information was entered based on the subject identification number they were assigned in order to protect patient privacy. The optic disc cube 200x200 protocol was used to image the right and left eye of patients meeting the aforementioned criteria. Only scan signal strengths of eight and above were used for this study. The average C/D ratio and the vertical C/D measurements were obtained from the Cirrus OCT ONH and RNFL OU analysis package.

Participants were then photographed with the Kowa Non-Myd Wx 3D retinal camera. The camera was set to take a stereoscopic image of the ONH. The patient was not dilated and was photographed under dark lighting conditions, promoting natural mydriasis. The Berezin Wheatstone Mini-scope was used if needed to aid in stereoscopic analysis of the ONH and evaluation of the average and vertical C/D measurements.

Two fourth year optometric students and one optometrist independently measured the average and vertical C/D ratios.

Results

Demographics

A total of 43 healthy subjects were enrolled in the study, for a total of 86 eyes. Of these 86 eyes, 7 were excluded due to the stereophotographs being deemed poor quality.

An additional 7 eyes were excluded for having OCT scans with scan qualities less than 8. A total of 72 eyes remained for the study. Age and sex data was not obtained for the subjects.

Analyses

Average C/D ratio and the vertical C/D ratio were analyzed separately, and then further divided and grouped by C/D ratio. For each subgroup, the mean, standard deviation, and intra-class correlation coefficient (ICC) was calculated for the difference between the OCT and the clinician's average assessment (CAA). In addition to these statistics, the ICC between the three clinicians was also averaged as a way to assess the variability amongst the clinicians. The results of these analyses can be seen in Table 1 below. Interpretation of the ICC is provided in Table 2 for reference. Bland-Altman plots were created to compare the difference between the OCT and the CAA for various C/D sizes. This type of plot charts the difference between two methods on the Y-axis and the unit analyzed on the X-axis. Frequently, horizontal lines are plotted for the mean and 2 standard deviations above and below the mean to help visualize overall agreement of the data. If the standard deviations are far apart, it indicates greater variability and less agreement. It needs to be clarified that the C/D size on the X-axis of the Bland-Altman plots in this study are the mean between the OCT and the CAA. The C/Ds were divided into subgroups based on their sizes as determined by the CAA, not the mean C/D size between the OCT and the CAA. This is why for several plots it appears to include C/Ds out of the range for that subgroup.

Statistics for the Difference between OCT and Clinician's Average Assessment										
	Sample size (n)		Mean		Std Dev		ICC		Mean ICC amongst clinicians	
	Avg C/D	Vertical C/D	Avg C/D	Vertical C/D	Avg C/D	Vertical C/D	Avg C/D	Vertical C/D	Avg C/D	Vertical C/D
All	72	72	0.06	0.03	0.09	0.08	0.89	0.88	0.82	0.87
C/D <0.3	25	24	0.01	-0.04	0.11	0.10	0.43	0.49	0.22	0.27
C/D 0.3<0.4	18	18	0.06	0.08	0.06	0.08	0.53	0.37	0.14	0.00
C/D 0.4<0.5	14	14	0.09	0.04	0.07	0.05	0.78	0.66	-0.08	-0.03
C/D 0.5+	15	16	0.09	0.04	0.04	0.04	0.53	0.30	0.06	0.02

Table 1. Statistics for the Difference between OCT and the Clinician's Average Assessment

Interpretation of ICC	
ICC	Agreement
1	Perfect agreement
0.99 to 0.81	Almost perfect agreement
0.80 to 0.61	Substantial agreement
0.60 to 0.41	Moderate agreement
0.40 to 0.21	Fair agreement
0.20 to 0.01	Slight agreement
0.0 to −0.1	Poor agreement

Table 2. Interpretation of ICC

Average C/D

The sample size included all 72 eyes for the analysis of the average C/D. The mean difference between the OCT and the CAA was 0.06. This can be interpreted as the OCT over-estimated the C/D by 0.06. The standard deviation within this group was 0.09. The ICC between the OCT and the CAA was 0.89, which can be interpreted as almost perfect agreement. The mean ICC between clinician's was 0.82, also demonstrating almost perfect agreement.

As can be seen below in Figure 1, when sorted by average C/D size as assessed by the CAA and then plotted with the OCT's assessment of that same nerve, there seems to be a greater difference as the C/D size increases (this was further analyzed as the C/D sizes were subdivided).

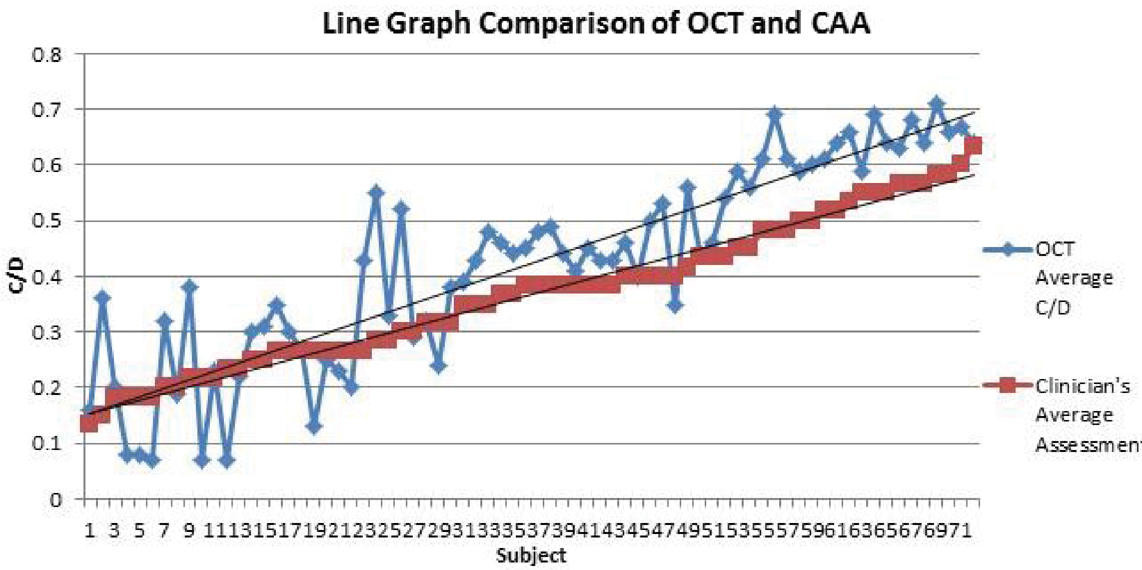

Figure 1. Line Graph Comparison of OCT and Clinician's Average Assessment (CAA).

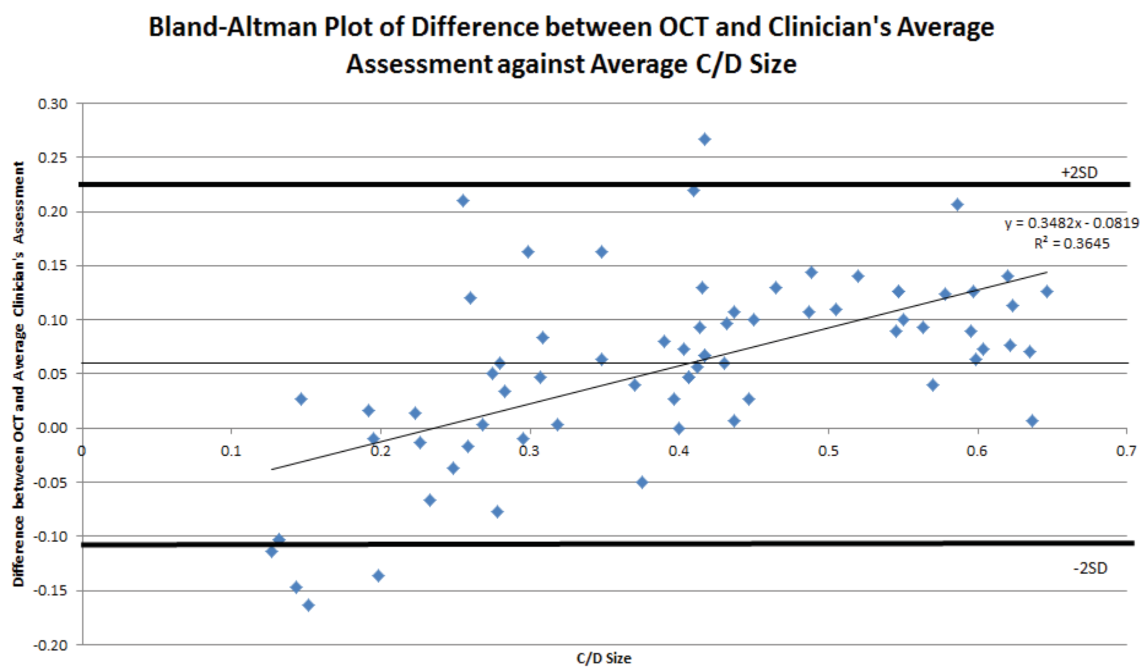

Figure 2. Bland-Altman plot of Difference between OCT and Clinician's Average Assessment against C/D Size. Mean difference: shown as single thin line at 0.06. 2 standard deviations (SD) above mean plotted at 0.22. 2 SD below mean plotted at -0.11. R^2=0.36.

The Bland-Altman plot in Figure 2 above plots the difference between the OCT and the CAA against the average C/D size. This plot shows most points are within 2 standard deviations of the mean. However, the points are spread fairly wide and loose, indicating the correlation between the OCT and the CAA is not as strong as the ICC may convey it is. The coefficient of determination (R^2) is 0.36, indicating the lack of a trend between the OCT and the CAA, or a greater variability in differences for a given C/D size between the OCT and the CAA. It is worth noting that it seems the OCT and the CAA does not differ when the average C/D is about 0.23, but few data points are grouped there. The trend below this C/D is the OCT underestimates average C/D size, and C/Ds over 0.23 are overestimated in size.

The average C/D subgroup of C/Ds less than 0.3 had a sample size of 25, representing almost 35% of the subjects. The mean difference between the OCT and the CAA was 0.01, with a standard deviation of 0.11. The ICC between OCT and CAA was 0.43, meaning there was a moderate agreement. Figure 3 below shows the Bland-Altman plot for the difference between the OCT and the CAA for average C/Ds less than 0.3. The plot demonstrates that the difference points are spread over a wider range, but the coefficient of determination (R^2) is 0.67, indicating a better trend and less variability in the difference between the OCT and CAA per C/D size. Again, C/Ds less than about 0.23 are underestimated and the C/Ds larger than this are overestimated. The median CAA C/D in this subgroup was 0.28 with a range of 0.15; the median OCT C/D in this subgroup was 0.23 but the range was 0.48. This is why the data points plotted are widely spread on the X-axis. Interestingly, the mean ICC between clinicians was only 0.21, showing marginally fair agreement amongst them.

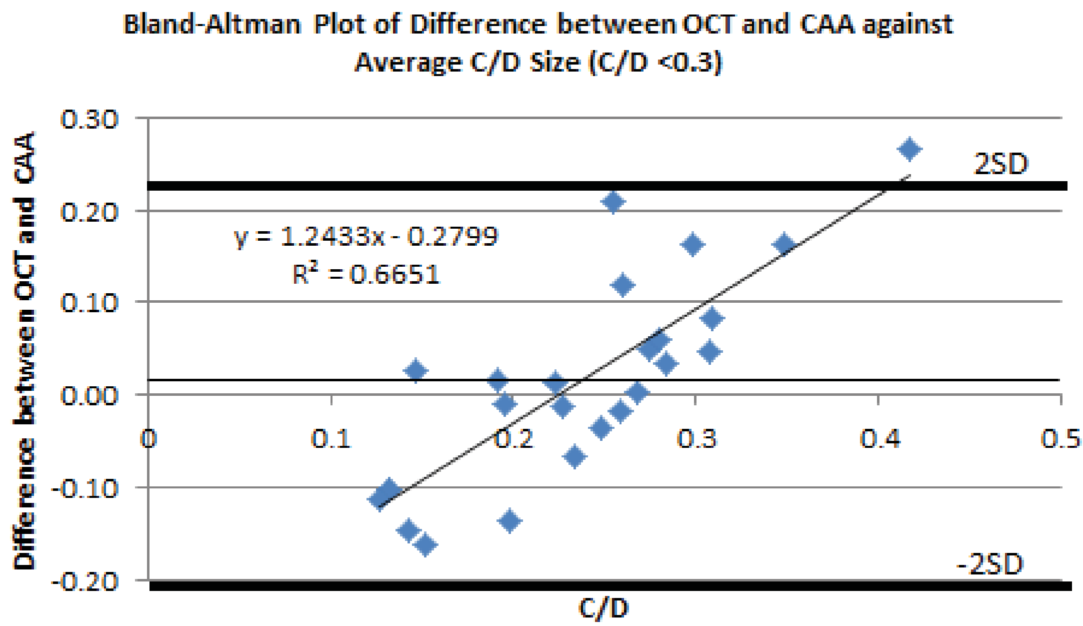

Figure 3. Bland-Altman plot of Difference between OCT and Clinician's Average Assessment against C/D Size (C/D <0.3). Mean difference: shown as single thin line at 0.01. 2 standard deviations (SD) above mean plotted at 0.22. 2 SD below mean plotted at -0.11. R^2=0.67.

The average C/D subgroup of C/Ds ranging from 0.3 to less than 0.4 had a sample size of 18, representing 25% of the subjects. The mean difference between the OCT and the CAA was 0.6, with a standard deviation of 0.06. There was moderate agreement between the OCT and CAA (ICC=0.53). Figure 4 below shows the Bland-Altman plot for the difference between the OCT and the CAA for average C/Ds ranging from 0.3 to less than 0.4. The plot demonstrates that the difference points are spread again over a wide range. The coefficient of determination (R^2) is 0.54, indicating a moderate trend and less variability in the difference between the OCT and CAA per C/D size. C/Ds less than about 0.32 are underestimated and the C/Ds larger than this are overestimated. The CAA for C/Ds in this subgroup were closer to 0.4 with the median C/D in this range being 0.37. Interestingly, the mean ICC between clinicians was 0.14, showing only slight agreement amongst them.

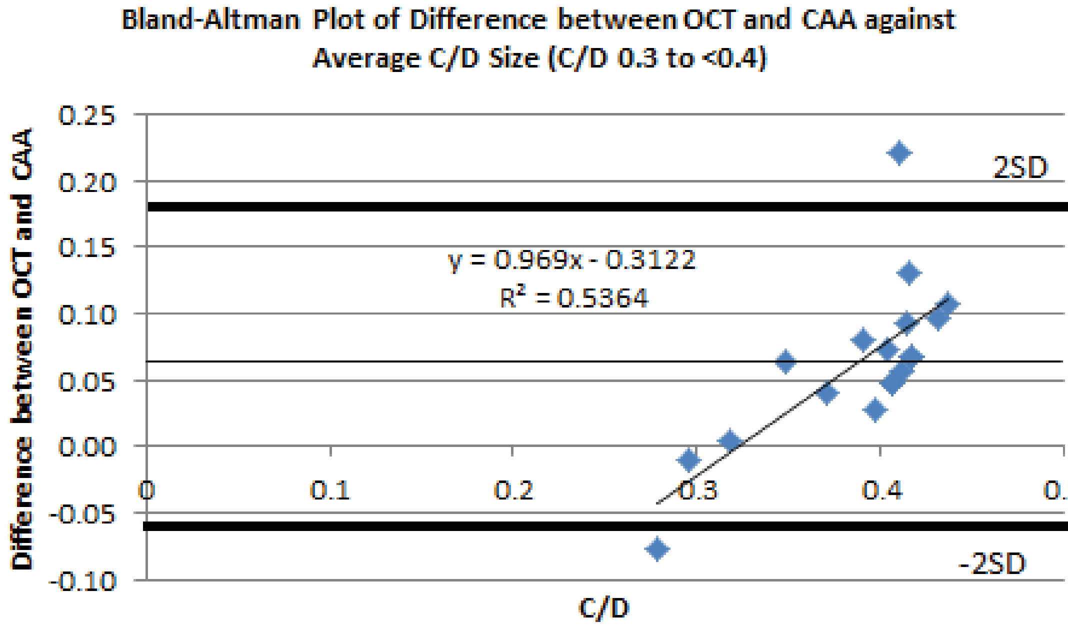

Figure 4. Bland-Altman plot of Difference between OCT and Clinician's Average Assessment against C/D Size (C/D 0.3 to <0.4). Mean difference: shown as single thin line at 0.06. 2 standard deviations (SD) above mean plotted at 0.18. 2 SD below mean plotted at -0.06. R^2=0.54.

The average C/D subgroup of C/Ds ranging from 0.4 to less than 0.5 had a sample size of 14, representing just over 19% of the subjects. The mean difference between the OCT and the CAA was 0.08, with a standard deviation of 0.07. The ICC between OCT and the CAA for this subgroup was the highest of all the average and vertical subgroups, 0.78 meaning there was substantial agreement. Figure 5 below shows the Bland-Altman plot for the difference between the OCT and the CAA for average C/Ds ranging from 0.4 to less than 0.5. The plot demonstrates that the difference points are spread again over a wide range. The coefficient of determination (R^2) is about 0.80, indicating a good trend and even less variability in the difference between the OCT and CAA per C/D size than previous subgroups. C/Ds within this subgroup are consistently overestimated by the OCT compared to the CAA. For further clarification, the C/D size on the X-axis is the mean between the OCT and the CAA. The median C/D by the CAA in this subgroup was 0.43 but the OCT median C/D was 0.53, consistent with the OCTs overestimation of this size C/Ds. Unfortunately, the mean ICC between clinicians assessing C/Ds in this subgroup was -0.08, indicating no agreement amongst them and possibly highlighting a weakness of the study.

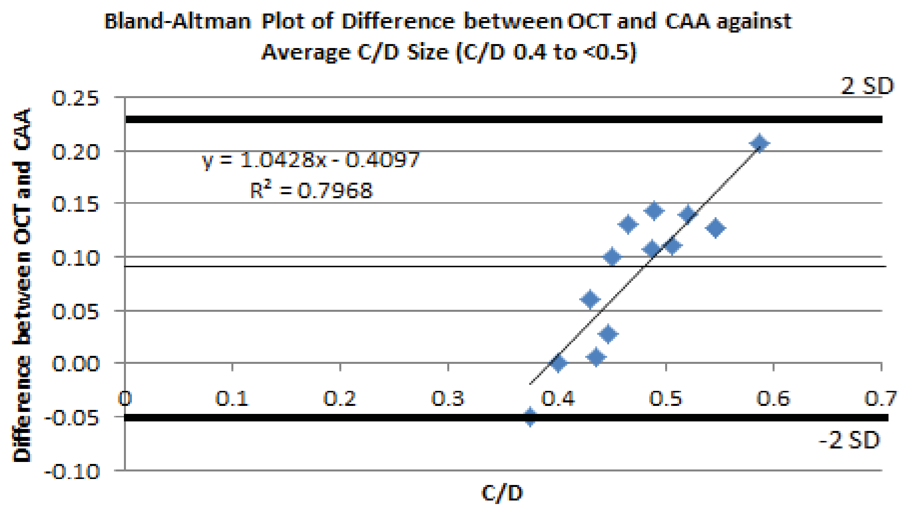

Figure 5. Bland-Altman plot of Difference between OCT and Clinician's Average Assessment against C/D Size (C/D 0.4 to <0.5). Mean difference: shown as single thin line at 0.08. 2 standard deviations (SD) above mean plotted at 0.23. 2 SD below mean plotted at -0.05. R^2=0.80.

The average C/D subgroup of C/Ds above 0.5 had a sample size of 15, representing almost 21% of the subjects. The mean difference between the OCT and the CAA was 0.09, with a standard deviation of 0.04. There was a drop in agreement between the OCT and CAA in this subgroup back to moderate agreement (ICC=0.53). Figure 6 below shows the Bland-Altman plot for the difference between the OCT and the CAA for average C/Ds above 0.5. The plot demonstrates that the difference points are spread almost evenly above and below the mean line. The coefficient of determination (R2) is essentially 0.00, indicating no trends in the difference between OCT and CAA for this size of C/Ds. It could be interpreted that for C/Ds above 0.5, the OCT will consistently over-estimate the C/D by 0.09 ± 0.01 (SE). The median C/D by the CAA in this subgroup was 0.55 and the OCT median C/D was 0.64, consistent with the OCTs

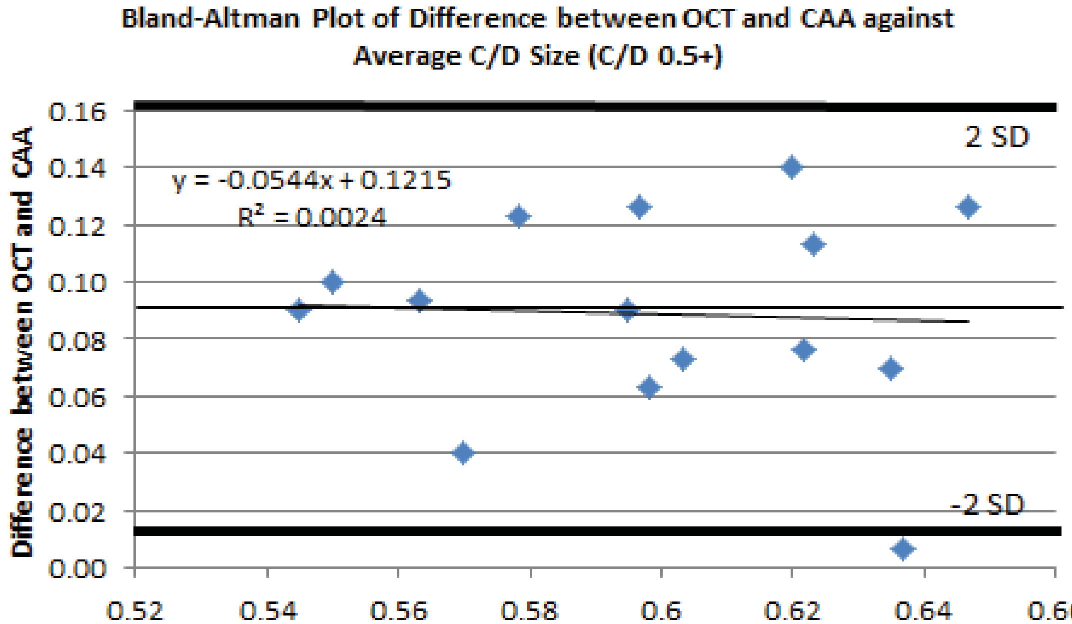

Figure 6. Bland-Altman plot of Difference between OCT and Clinician's Average Assessment against C/D Size (C/D 0.5+). Mean difference: shown as single thin line at 0.09. 2 standard deviations (SD) above mean plotted at 0.16. 2 SD below mean plotted at -0.017. R^2=0.00.

overestimation of these C/Ds of 0.09. The mean ICC between clinicians assessing C/Ds in this subgroup was 0.06, again showing no agreement amongst the three clinicians.

Vertical C/D

The sample size included all 72 eyes for the analyses of the vertical C/D. The mean difference between the OCT and the CAA was 0.03. This can be interpreted as the OCT overestimated the vertical C/D by 0.03. The standard deviation within this group was 0.08. The ICC between the OCT and the CAA was 0.88, which can be interpreted as almost perfect agreement. The mean ICC between clinician's was 0.86, demonstrating almost perfect agreement. Below in Figure 7, when sorted by vertical C/D size as assessed by the CAA and then plotted with the OCT's assessment of that same nerve, there seems to be a minor difference as the C/D size increases (this was later analyzed).

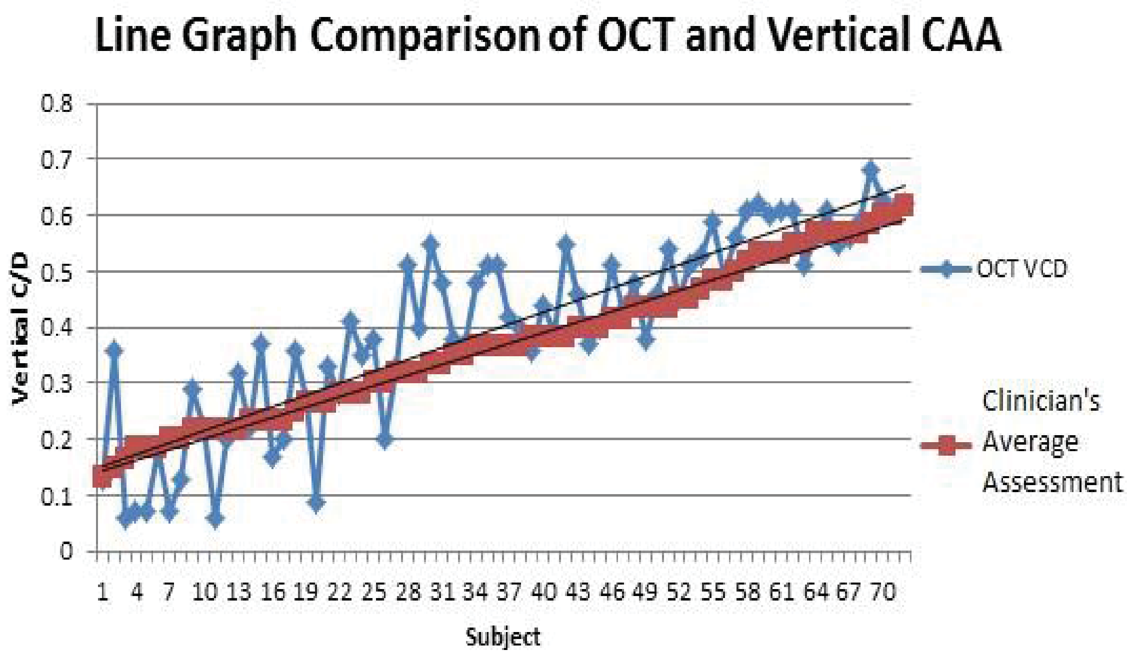

Figure 7. Line Graph Comparison of OCT and Vertical Clinician's Average Assessment (CAA).

The Bland-Altman plot shown below in Figure 8 plots the difference between the OCT and the CAA against the vertical C/D size. This plot shows most points are within 2 standard deviations of the mean. However, the points are spread wide and loose like the average C/D Bland-Altman plot, indicating the correlation between the OCT and the vertical CAA is not as strong as the ICC makes it appear, similar to the pattern seen with the average C/D group. The coefficient of determination (R^2) is about 0.20, indicating an even worse trend between the OCT's vertical C/D and the CAA vertical C/D than the average C/D. The X-intercept is around 0.25, which is where the OCT and the CAA do not differ. The trend below this C/D is the OCT under-estimates vertical C/D size, and C/Ds over 0.25 are over-estimated in size.

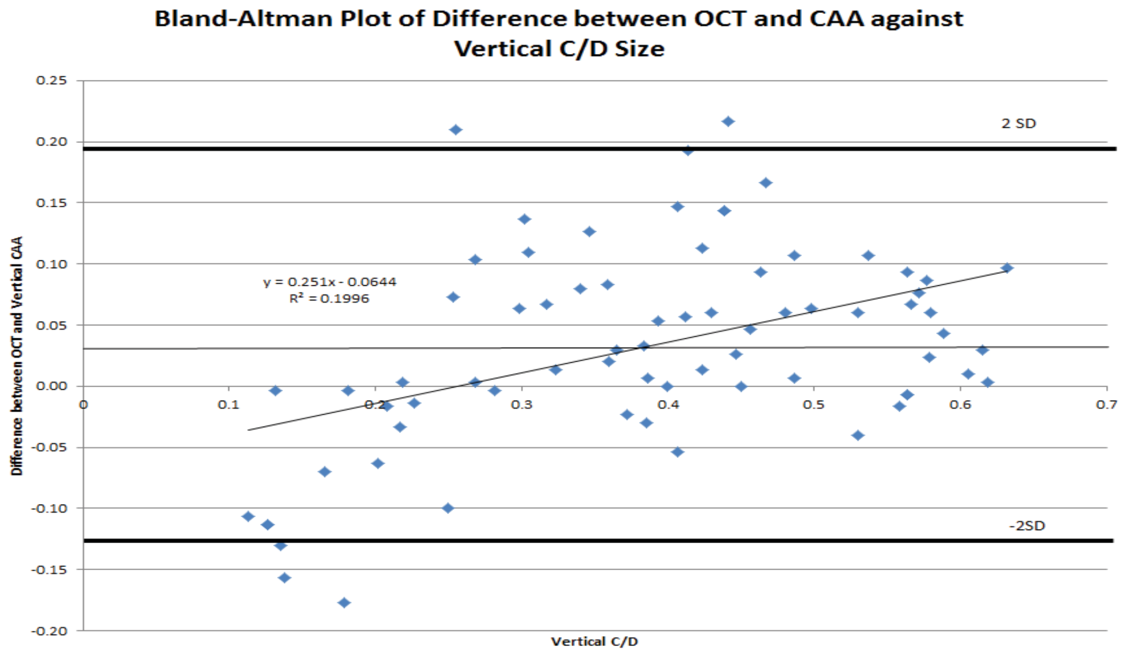

Figure 8. Bland-Altman plot of Difference between OCT and CAA against Vertical C/D Size. Mean difference: shown as single thin line at 0.03. 2 standard deviations (SD) above mean plotted at 0.197. 2 SD below mean plotted at -0.13. R^2=0.20.

The vertical C/D subgroup of C/Ds less than 0.3 had a sample size of 24, representing almost one-third of the subjects. The mean difference between the OCT and the vertical CAA was 0.00, with a standard deviation of 0.10. The ICC between OCT and the CAA here was 0.49, showing moderate agreement. Figure 9 below shows the Bland-Altman plot for the difference between the OCT and the vertical CAA for vertical C/Ds less than 0.3. The plot demonstrates that the difference points are spread over a wide range. The coefficient of determination (R^2) is 0.65, indicating a much better trend and less variability in the difference between the OCT and vertical CAA per C/D size. Vertical C/Ds less than about 0.25 are underestimated and the C/Ds larger than this are overestimated. The median vertical CAA C/D in this subgroup was 0.22 with a range of 0.15; the median OCT C/D in this subgroup was 0.21 but the range was 0.35 (more than twice the range of the vertical CAA). This is why the difference plot is widely spread on

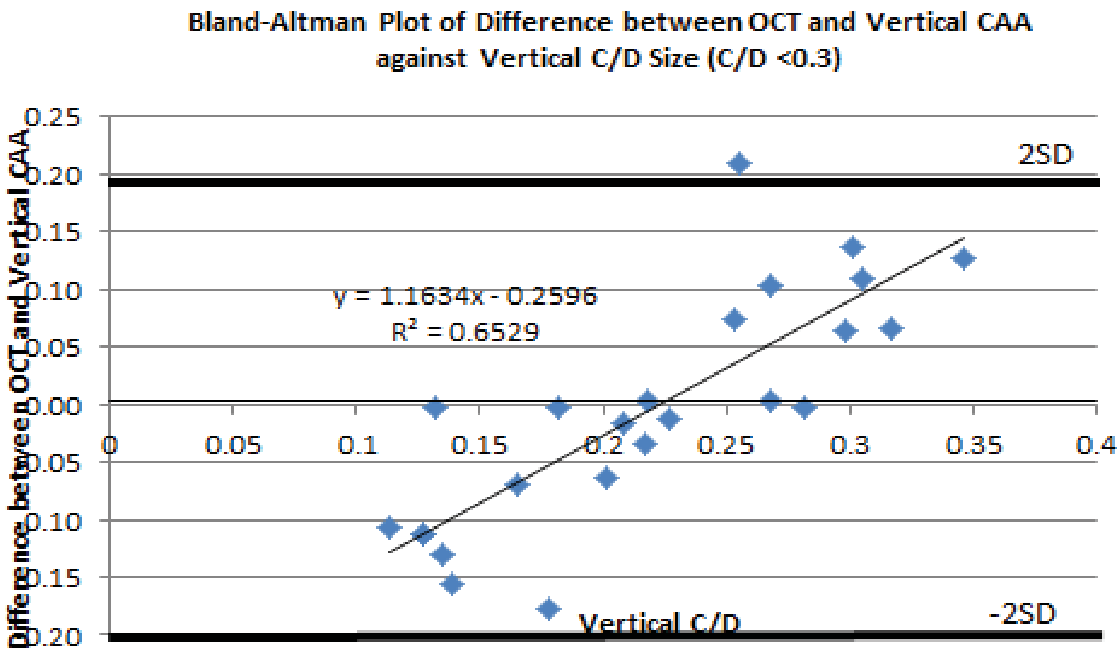

Figure 9. Bland-Altman plot of Difference between OCT and CAA against Vertical C/D Size (C/D <0.3). Mean difference: shown as single thin line at 0.00. 2 standard deviations (SD) above mean plotted at 0.197. 2 SD below mean plotted at -0.21. R^2=0.65.

the X-axis. The mean ICC between clinicians was only 0.27, showing fair agreement amongst the clinicians.

The vertical C/D subgroup of C/Ds ranging from 0.3 to less than 0.4 had a sample size of 18, representing about 43% of the subjects. The mean difference between the OCT and the vertical CAA was 0.08, with a standard deviation of 0.08. The ICC for this subgroup was 0.37, indicating only fair agreement. Figure 10 below shows the Bland-Altman plot for the difference between the OCT and the vertical CAA for vertical C/Ds between 0.3 and less than 0.4. The plot demonstrates that the difference points are spread over a wide range still. The coefficient of determination (R^2) is 0.67, indicating about the same trend and variability in the difference between the OCT and vertical CAA per C/D size as small vertical C/Ds. Vertical C/Ds less than about 0.33 are underestimated and the C/Ds larger than this are overestimated. The median vertical CAA C/D in this subgroup was 0.35 with a range of 0.08; the median OCT C/D in this subgroup was 0.41 and the range was 0.35 (more than four times larger than the range of the vertical CAA). This is why the difference plot is more widely spread out across the X-axis. The mean ICC between clinicians was essentially 0.00, showing no agreement amongst the clinicians.

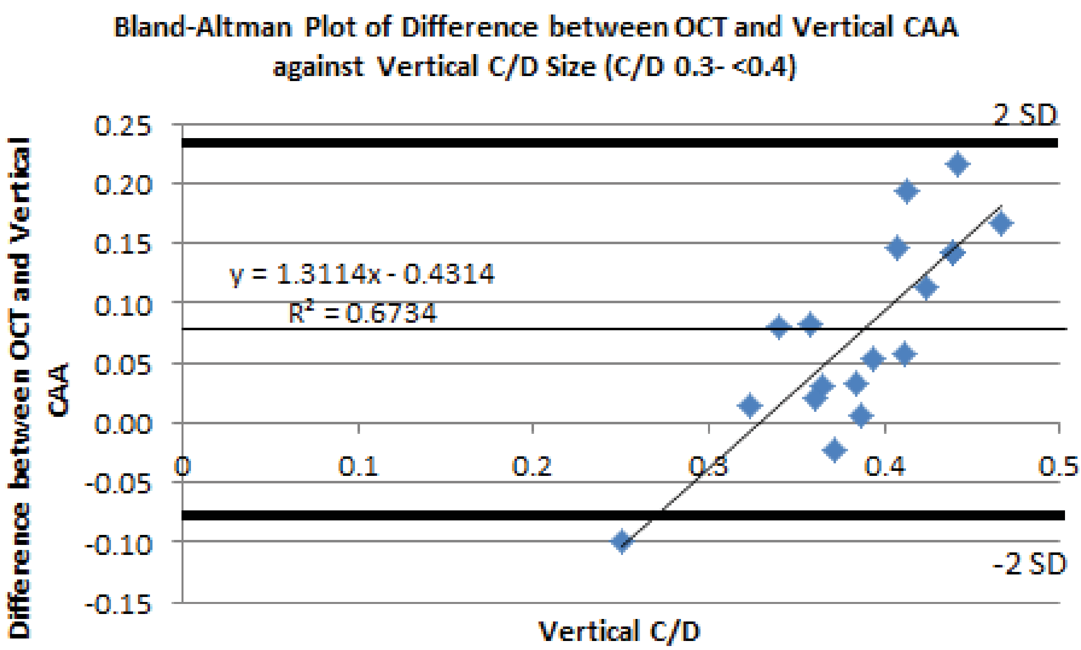

Figure 10. Bland-Altman plot of Difference between OCT and CAA against Vertical C/D Size (C/D 0.3-<0.4). Mean difference: shown as single thin line at 0.08. 2 standard deviations (SD) above mean plotted at 0.24. 2 SD below mean plotted at -0.09. R^2=0.67.

The vertical C/D subgroup of C/Ds ranging from 0.4 to less than 0.5 had a sample size of 14, representing about 19% of the subjects. The mean difference between the OCT and the vertical CAA was 0.04, with a standard deviation of 0.05. This subgroup had the highest ICC between the OCT and the CAA for vertical C/Ds, with an ICC of 0.66 (substantial agreement). Figure 11 below shows the Bland-Altman plot for the difference between the OCT and the vertical CAA for vertical C/Ds between 0.4 and less than 0.5. The plot demonstrates that the difference points are spread over a narrower range than before, indicating less of a range difference between the OCT and the CAA. The coefficient of determination (R^2) is 0.58, indicating a weaker trend and greater variability in the difference between the OCT and vertical CAA per C/D size than smaller vertical C/Ds. The plot shows that most C/Ds larger than 0.4 are now overestimated by the OCT. The median vertical CAA C/D in this subgroup was 0.43 with a range of 0.08; the median OCT C/D in this subgroup was 0.47 and the range was 0.22 (almost three times larger than the range of the vertical CAA). This is a smaller difference in the ranges compared to smaller C/Ds, which is reflected in the steeper slope of the regression line. The mean ICC between clinicians was -0.02, again showing no agreement amongst the clinicians.

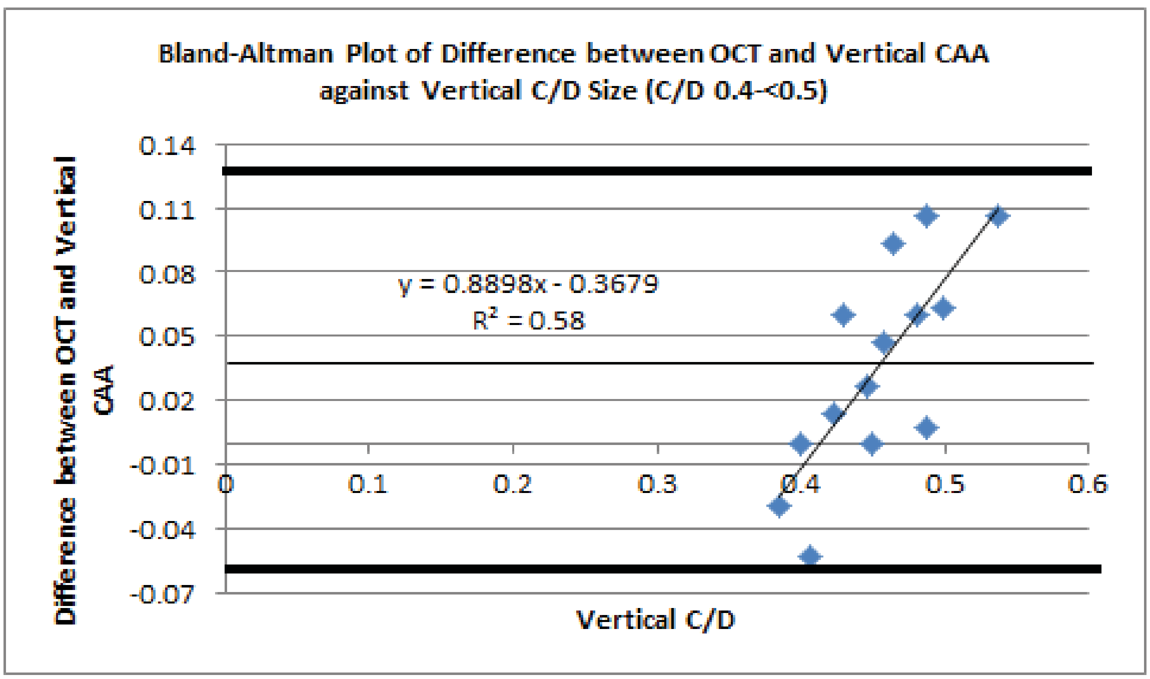

Figure 11. Bland-Altman plot of Difference between OCT and CAA against Vertical C/D Size (C/D 0.4-<0.5). Mean difference: shown as single thin line at 0.04. 2 standard deviations (SD) above mean plotted at 0.13. 2 SD below mean plotted at -0.06. R^2=0.58.

The vertical C/D subgroup of C/Ds from 0.5 and larger had a sample size of 16, representing about 38% of the subjects. The mean difference between the OCT and the vertical CAA was 0.04, with a standard deviation of 0.04. Similar to this size C/D subgroup for the average C/Ds, the ICC here fell to 0.3 (fair agreement). Figure 12 below shows the Bland-Altman plot for the difference between the OCT and the vertical CAA for vertical C/Ds 0.5 and larger. The plot demonstrates that the difference points are spread over a broader range any of the other C/Ds, indicating a very wide range difference between the OCT and the CAA. The coefficient of determination (R^2) is about 0.06, indicating practically no trend and great variability in the difference between the OCT and vertical CAA per C/D. The plot shows that C/Ds smaller than 0.58 are minimally underestimated by the OCT and vice versa. The median vertical CAA C/D in this subgroup was 0.57 with a range of 0.12; the median OCT C/D in this subgroup was 0.61 and the range was 0.17. This range variation can be seen in the plot as points spread out across the X-axis. The mean ICC between clinicians was 0.02, showing slight agreement amongst the clinicians.

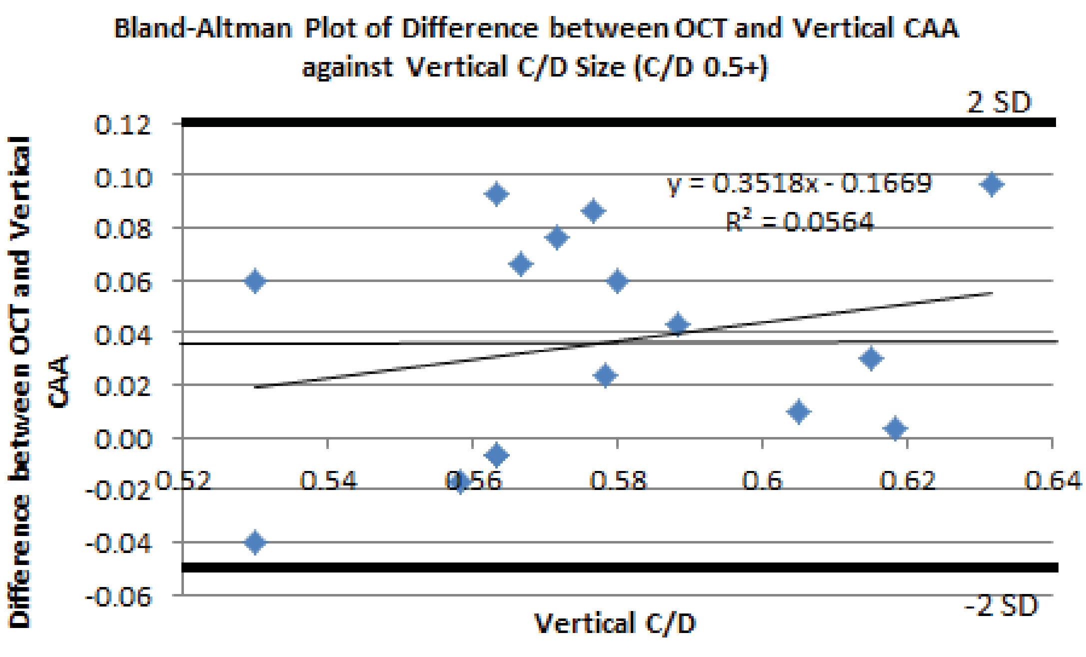

Figure 12. Bland-Altman plot of Difference between OCT and CAA against Vertical C/D Size (C/D 0.5+). Mean difference: shown as single thin line at 0.04. 2 standard deviations (SD) above mean plotted at 0.13. 2 SD below mean plotted at -0.05. R^2=0.06.

Discussion

The OCT is a helpful clinical tool that can assess the C/D ratio of a patient. It is important to understand the correlation this objective measure has to the stereoscopic view of an examiner. Viewing the ONH stereoscopically is important clinically because the cup is not limited to the area of pallor viewed in a two-dimensional photograph. Also stereoscopic evaluation and measurement of the C/D has been proven to be more consistent between examiners than using a direct ophthalmoscope (Rumsey et al, 2000). Considering the OCT and stereoscopic examination, it is helpful to have both methods available since there is no uniform technique to prevent inter-observer variability when measuring the C/D.

There are many variables that exist when evaluating the ONH and monitoring it over time for change. Inter-observer variability, the method of measurement used, peripapillary changes, and variations in normal physiology, for example a tilted disc, all play a factor in complicating the assessment of the optic nerve. The Cirrus OCT uses the edge of Bruch's membrane to determine the border of the optic nerve; the method this OCT uses for determining the cup margin have not been disclosed by Zeiss. It has been noted that clinicians often take into account the contrast between optic nerve tissue and surrounding peripapillary tissue when determining the disc border (Sharma et al, 2011). This method is unlikely to be as consistent as the technique the OCT uses. The clinician frequently has to extrapolate the cup margin when overlying vessels or vitreous tissue obscures the borders. The Cirrus HD-OCT is more capable of differentiating these different tissues than previous OCT models but still can make incorrect measurements. Errors were found to be more frequent in myopes, eyes with peripapillary atrophy, high myopia, greater axial length, eyes with vitreous opacities and acute cup slope angles (Hwang et al, 2012) Overall though, the Cirrus HD-OCT has been shown to have excellent intra-visit and inter-visit reproducibility of optic nerve head parameters (Mwanza et al, 2011). This is beneficial for patients that are co-managed by practitioners in different locations. The practitioners may subjectively judge the C/D ratios differently depending on training and patient population but the Cirrus HD-OCT should be consistent.

The trend in the data for average C/Ds seems to be the OCT overestimated the C/D with increasing C/D size and underestimated them when smaller than about 0.2. The mean difference between the OCT and the CAA for average C/Ds increased in successive subgroups. However, the standard deviation of the difference showed a general decline as the C/Ds grew larger, indicating less variability and more consistency between assessments of both the OCT and the CAA as C/D size increased. Overall, the OCT overestimated the average C/D compared to the CAA by 0.06.

The trend isn't quite as clear with vertical C/Ds as it was for the average C/Ds. The OCT tended to underestimate vertical C/Ds less than 0.3, but only nominally (-0.04). The greatest difference was in the 0.3 to less than 0.4 subgroup with the OCT overestimating the vertical C/D by 0.08. The rest of the subgroups also were overestimated but by only 0.04. Like the average C/D standard deviation, the standard deviation of differences decreased with increasing C/D size, implying less variation and more consistency amongst the OCT and the CAA. Other studies have also found that it is easier for the OCT to estimate larger vertical C/Ds; this was attributed to steeper sloping walls of the cup (Savini et al, 2013). Overall, the OCT overestimated the vertical C/D by

0.03, half of what it overestimated the average C/D. This implies that in general, the OCT is closer to our clinical assessment of the vertical C/D than the average C/D. There is limited clinical usefulness of assessing the average C/D since one of the most common optic neuropathies managed by optometrists, glaucoma, increase vertical C/D early in the disease.

The ICC between the OCT and the CAA for all the average C/Ds misleadingly shows almost perfect agreement. When the ICC in each subgroup is looked at, it seems the best agreement can be interpreted as substantial for average C/Ds 0.4 to less than 0.5. This is interesting and in contrast with the mean difference between OCT and the CAA in this group of 0.09, which was one of the highest differences for both average and vertical C/D subgroups. The lowest ICC for the average C/Ds was in the subgroup of C/Ds less than 0.3 (ICC=0.43, barely moderate agreement). Bland-Altman plots for all subgroups show relatively large areas plotted between the lines marking 2 SDs from mean. Ideally, if there was better agreement, these lines would be closer to the mean.

The ICC between all of the vertical C/Ds is also misleading, with an ICC of 0.88 (about the same as the average C/Ds), implying almost perfect agreement. The greatest agreement for vertical C/D subgroups was also in the 0.4 to less than 0.5 subgroup (like the average C/D), being 0.66 and interpreted as substantial agreement. The lowest ICC for both the average and vertical C/D groups was in the vertical C/D subgroup of C/Ds larger than 0.5 (ICC=0.3, fair agreement). Again, lines plotted 2 SD from the mean on all of the vertical C/D subgroup Bland-Altman plots are relatively wide, showing relatively poor agreement.

There are weaknesses with this study that need to be identified. This study analyzed healthy ONHs, which were all of young, healthy optometry students. The subject population was very homogenous and did not include a good representation of age or race. Although this study was designed to include only health subjects, more clinically useful information may have been obtained if glaucomatous eyes were included for further comparison. Other studies have been published doing exactly this.

Another weakness of this study was in the small number of clinicians used to determine the CAA. This is because of poor inter-observer agreement, which may have been improved with more clinicians contributing to the CAA. Ideally, Fleiss' kappa coefficient would have been measured to better assess the intra-observer agreement, but instead the mean of the ICC between clinicians was used. At first glance, the mean ICC between clinicians for all of the average C/Ds and all of the vertical C/Ds appears to be very good (0.82 and 0.87, respectively). However, once the C/Ds were divided into subgroups, the mean of the ICC plummets. The best agreement between clinicians was for C/D sizes less than 0.3, for which the agreements were fair. The clinicians had only poor or slight agreement for the rest of the C/Ds. This calls into question the validity of using the CAA as the standard to compare the OCT against. One possible reason for the poor mean ICC between clinicians was simply experience level, as two of them are still students and the other is a residency trained optometrist. The study by Spalding et al (2000) (cited earlier), which evaluated the agreement amongst optometrists in the evaluation of the optic nerve, showed that residency trained optometrists agree more with other residency trained optometrists. This same study also showed that there is better agreement when the clinicians have similar experience evaluating glaucomatous nerves.

Considering the results of Spalding's study, it could be said that not only was the mean ICC between clinicians in our study poor because of the number of clinicians, but possibly due to the difference in training and experience.

In conclusion, our study shows that there was disagreement between clinicians and the OCTs assessment of both average and vertical C/Ds. This disagreement was greater for larger C/Ds, but was consistently greater. It also demonstrated that OCT evaluation of the ONH is not sufficient alone to accurately determine the C/D, but together with ophthalmoscopic evaluation of the optic nerve can provide one more piece of data when assessing difficult to judge C/Ds.

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APPENDIX A

IRB APPROVAL FORM

Ferris State University

Institutional Review Board (FSU - IRB)
Office of Academic Research
Ferris State University
1201 S. State Street-CSS 310 H
Big Rapids, MI 49307
(231) 591-2553
IRB@ferris.edu

To: Dr. Brian McDowell, Mr. Mathew Tholl and Mr. Mark Debano, Jr.
From: Dr. John Pole, Interim IRB Chair
Re: IRB Application #130801 (Title: *Comparison of Cup-to-Disc Ratios as measured using Ocular Coherence Tomography and Stereoscopic Fundus Photography*)
Date: August 22, 2013

The Ferris State University Institutional Review Board (IRB) has reviewed your application for using human subjects in the study, "*Comparison of Cup-to-Disc Ratios as measured using Ocular Coherence Tomography and Stereoscopic Fundus Photography*" (#130801) and approved it as *expedited – 2D* from full committee review. This approval has an expiration date of one year from the date of this letter. As such, you may collect data according to procedures in your application until *August 22, 2014.* It is your obligation to inform the IRB of any changes in your research protocol that would substantially alter the methods and procedures reviewed and approved by the IRB in this application. Your application has been assigned a project number (#130801) which you should refer to in future applications involving the same research procedure.

We also wish to inform researchers that the IRB requires follow-up reports for all research protocols as mandated by Title 45 Code of Federal Regulations, Part 46 (45 CFR 46) for using human subjects in research. We will send a one-year reminder to complete the final report or note the continuation of this study. The final-report form is available on the IRB homepage. Thank you for your compliance with these guidelines and best wishes for a successful research endeavor. Please let us know if the IRB can be of any future assistance.