Stereoscopic Analysis of Optic Nerve Head Parameters in Primary Open Angle Glaucoma: The Glaucoma Stereo Analysis Study

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Abstract

Purpose: The Glaucoma Stereo Analysis Study (GSAS), a cross sectional multicenter collaborative study, used a stereo fundus camera to assess various morphological parameters of the optic nerve head (ONH) in glaucoma patients and investigated the relationships between these parameters and patient characteristics.

Subjects and Methods: The study included 187 eyes of 187 subjects with primary open angle glaucoma or normal tension glaucoma (male: female = 100:87, age = 61 ± 9 years). Stereo pairs of ONH photographs were made with a stereo fundus camera (nonmyd WX). ONH morphological parameters were calculated with prototype analysis software. In addition to 35 standard parameters, we defined three novel parameters: disc tilt angle, rim decentering, and the absolute value of rim decentering. The correlation between each parameter and patient characteristics was analyzed with Spearman’s rank correlation coefficient.

Results: Patient characteristics included refractive error of −3.38 ± 3.75 diopters, intraocular pressure (IOP) of 13.6 ± 2.6 mmHg, and visual field mean deviation (MD) of −4.71 ± 3.26 dB. Representative ONH parameters included a horizontal disc width of 1.66 ± 0.28 mm, vertical disc width of 1.86 ± 0.23 mm, disc area of 2.42 ± 0.63 mm², cup area of 1.45 ± 0.57 mm², and cup volume of 0.31 ± 0.22 mm³. Correlation analysis revealed significant negative associations between vertical cup-to-disc ratio (0.82 ± 0.08) and MD (r = −0.40, P < 0.01) and between disc tilt angle (10.5 ± 12.5 degrees) and refractive error (r = −0.36, P < 0.01). Seventy-five percent of the eyes had a positive value for rim decentering (0.30 ± 0.42), indicating that rim thinning manifested more often as an inferior lesion than a superior lesion.

Conclusion: We used stereoscopic analysis to establish a database of ONH parameters, which may facilitate future studies of glaucomatous changes in ONH morphology.

Introduction

Glaucoma is characterized by visual field defects that correspond to damaged areas of the optic nerve head (ONH). It affects over 70 million people worldwide, and is the second most common cause of blindness [1,2]. Generally, changes in ONH morphology, including thinning of the neuronal rim and enlargement of the ONH excavation, precede the progress of visual field defects. Morphological changes in the ONH are therefore considered important early biomarkers of GON and GON progression [4–6]. When identification of morphological changes is included in mass examinations and screenings, it has a positive effect on the early diagnosis of glaucoma [7,8]. Observation of the ONH remains a key part of...
Subjects and Methods

stereoscopic viewing [13]. Of glaucoma may be underestimated because of the difficulty of copy or a subjective examination, ONH cupping and the severity identifying the effects of structural changes on visual function the progression speed of glaucomatous visual field defects differed ONH types using Nicolela’s classification method, we found that important signs of risk [9]. In a previous study of glaucomatous follow-up care for glaucoma. Occurrences of rim notch, thinning of the local rim and enlargement of the ONH cup are especially important signs of risk [9]. In a previous study of glaucomatous ONH types using Nicolela’s classification method, we found that the progression speed of glaucomatous visual field defects differed with ONH types [10]. Identifying certain patterns of glaucomatous ONH morphology may improve diagnostic accuracy and aid in identifying the effects of structural changes on visual function [11,12]. However, when the ONH is assessed with ophthalmoscopy or a subjective examination, ONH cupping and the severity of glaucoma may be underestimated because of the difficulty of stereoscopic viewing [13].

Topographic analysis with a simultaneous stereo fundus camera (nonmyd WX, Kowa Company, Ltd., Japan) is a noninvasive, noncontact imaging technique that does not require pupillary mydriasis. Its reliability has been demonstrated in a previous paper [14]. It is therefore a promising tool for the assessment of ONH morphology. The Glaucoma Stereo Analysis Study (GSAS) is a multicenter study using this technique to assess various morphological parameters of the ONH in Japanese glaucoma patients. In this, the first report from GSAS, we established a database of various ONH parameters.

Subjects and Methods

This study (The Glaucoma Stereo Analysis Study: GSAS) was a cross sectional, multicenter collaborative study. It was approved by the Institutional Review Boards of the Tohoku University Graduate School of Medicine, Shimane University Faculty of Medicine, Fukui-ken Saiseikai Hospital, Sapporo Teishin Hospital and the Hospital of St. Marianna University School of Medicine. The patients, whose ages ranged from 30 to 80 years, underwent full clinical ophthalmologic evaluations, including testing for visual acuity, refractive error, and intraocular pressure (IOP) with Goldmann applanation tonometry, as well as slit lamp and fundus examinations. At least one measurement of pre-treatment IOP (baseline IOP) was obtained retrospectively. Pre-surgical data on refractive error was also collected from eyes that had undergone refractive procedures such as cataract surgery. Visual field examinations with the Humphrey visual field analyzer (HFA; Carl Zeiss Meditec Inc., Dublin, California) were performed on all subjects within 6 months of recruitment (SITA standard, 30–2 or 24–2). Data from at least six HFA examinations performed over at least the previous three years was also collected retrospectively for each patient. Only reliable visual field data were used, i.e., from examinations with less than 20% false positives, less than 20% false negatives and less than 33% fixation losses. The mean deviation (MD) slope was calculated from these data.

Glaucoma diagnosis was based on the finding of glaucomatous visual field defects in reliable data from an HFA examination, with corresponding GON. GON was defined as an enlarged vertical cup-to-disc (C/D) ratio, narrow neuroretinal rim (rim) width, notching, and nerve fiber layer defects.

Additional inclusion criteria included: 1) best corrected visual acuity of 0.155 or better (LogMAR); 2) no congenital ONH anomalies, 3) ONH size within the typical normal range, defined as a disc-macula distance to disc diameter (DM/DD) ratio between approximately 2.4 and 3.0, 4) no clinically apparent secondary cause of glaucoma and no other disease affecting the visual field, 5) no history of intraocular surgery other than cataract or glaucoma surgery, 6) no history of cataract or glaucoma surgery in the previous three years, and 7) glaucomatous visual field loss more than $-12\,\text{dB}\,\text{MD}$. If both eyes met the inclusion criteria, the eye with more advanced glaucoma was selected.

A summary of the inclusion criteria is shown in Table 1.
Analysis of optic nerve head topography

Stereo fundus images of the ONH were obtained with a commercially available simultaneous stereo fundus camera (nonmyd WX). The nonmyd WX produces nonmydriatic fundus stereographs, as well as simultaneous right and left parallaxic images, by using a single optical system to handle light paths in two directions [14]. The built-in software (VK-2 WX, prototype version, Kowa Company, Ltd., Japan) automatically calculates ONH morphological parameters based on manually-set contour lines for the ONH disc and cup, which in this study were determined by one of the authors (M.T.) while viewing the images stereoscopically. This determination was made according to the recommendations of the Japan Glaucoma Society Guidelines for Glaucoma, 3rd Edition [15,16]. The contour of the disc was delineated by the inner margin of Elschnig’s scleral ring, and the contour of the cup was delineated by the outer margin of the cup, which was indicated by the bending of the ONH vessels at the rim. The observer determined several points on the contour (typically 8–14), and the contour line was then automatically generated by software spline interpolation. Parameters nonmyd WX included vertical C/D ratio, upper rim width, lower rim width, cup area, disc area, rim area, C/D area ratio, rim-to-disc (R/D) area ratio, sectional R/D ratio, cup volume, disc volume, rim volume, mean cup depth, maximum cup depth, height variation contour and disc damage likelihood scale (DDLS) stage. Measurements for the area and volume of the cup, disc and rim are illustrated in Figure S1.

Figure 1. Histograms of ocular characteristics of the subjects. IOP: intraocular pressure, MD: mean deviation

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Depth value maps, necessary to determine parameters such as disc volume and mean cup depth, were generated based on the disparity between the right and left images of the stereo image pair with a stereo matching technique. Area and volume were calculated using three-dimensional analysis software (VK-2 WX) with correction for magnification. This correction, based on a modification of Littman’s method, was performed after entering the refractive error and corneal curvature of each eye into the software. The vertical and horizontal C/D ratios were defined as the ratio of the maximal vertical or horizontal diameter of the cup to maximal vertical or horizontal diameter of the disc. The aspect ratio was calculated by dividing the length of the largest diameter of the disc by the diameter perpendicular (Figure S2). DDLS stage (9 stages; 0a, 0b, 1, 2, 3, 4, 5, 6, 7) is a diagnostic parameter proposed by Bayer et al. that provides an estimation of glaucomatous disc damage [17,18]. Analysis of the sectorial rim of the ONH was performed as shown in Figure S3.

In this study, we defined three novel parameters, disc tilt angle, rim decentering, and the absolute value of rim decentering. Rim decentering was calculated with the following formula: rim decentering = (superotemporal rim area − inferotemporal rim area)/superotemporal rim area + inferotemporal rim area (Figure S3). For the statistical analysis, absolute values for rim decentering were also determined. Disc tilt angle was defined as the degree of the angle between the horizontal plane and the line drawn from the temporal to the nasal disc edge, passing through the center of the ONH (Figure S4).

Statistical analysis
Statistical analysis was performed with JMP pro 10.02 (SAS Institute Inc.) for Windows. Continuous variables were expressed as mean values ± standard deviation (SD). The Spearman’s rank correlation coefficient was used to determine correlations between the patients’ characteristics and the measured ONH parameters. In our analysis, ordinal data were treated as continuous data. The level of significance was set at 0.05 in all statistical tests.

Results
The detailed characteristics of the 187 subjects included in this study are shown in Table 2. The average patient age was 61.4 ± 9.3 years. The sex ratio (male to female) was 100:87, with no significant difference in age between the sexes (60.5 ± 0.9, 62.4 ± 1.0, P = 0.16, t-test, respectively). The average spherical equivalent refractive error was −3.38 ± 3.75 diopters (if a subject had undergone cataract surgery, pre-surgical refractive error was used to calculate the average), indicating that myopia was common among the subjects in this study. Compared to the baseline (16.9 ± 4.3 mmHg), IOP was lower on the test day (13.6 ± 2.6 mmHg, P < 0.01, paired t-test). The average MD in these eyes was −4.71 ± 3.26 dB. Retrospective data for the follow-up period (82.3 ± 42.7 months, range 36–188 months) showed that the average MD slope was −0.12 ± 0.38 dB/year, with 12% (23 eyes) of subjects progressing at a rate faster than −0.50 dB/year. Histograms are shown in Figure 1.

Average ONH topographic parameters are shown in Table 3. The average disc horizontal and vertical widths were 1.66 ± 0.28 mm and 1.86 ± 0.23 mm, respectively. The average disc aspect ratio was 1.14 ± 0.18. The average size of the disc cup was large (area: 1.45 ± 0.57 mm², volume: 0.31 ± 0.22 mm³) and the average rim of the ONH was thin (area: 0.97 ± 0.27 mm², volume: 0.17 ± 0.10 mm³) in the GON patients. The average DDLS stage (3.77 ± 0.95) indicated that the rim of the ONH had thinned and had defects. We found that 75% of subjects had a positive value (0.30 ± 0.42) for rim decentering, one of the new parameters in this study, indicating that damage to the ONH occurred at the lower side of the rim. The average disc tilt angle was 10.5 ± 12.5 degrees.

To investigate the relationship between ONH morphological parameters, the characteristics of the patients and visual field defects, we used Spearman’s rank correlation coefficient (Table 4). Vertical C/D ratio and rim area were significantly correlated to visual field loss (MD) (r = −0.40, P < 0.01, r = 0.40, P < 0.01). Disc tilt angle was significantly correlated to age and spherical equivalent refractive error (r = −0.30, P < 0.01, r = −0.36, P < 0.01). We also performed a multiple regression analysis, assigning tilt angle as the response variable and each of the latter two parameters as explanatory variables, to determine the strongest correlation between disc tilt angle, age and refractive error. The standardized partial regression coefficient (β value) for age was −0.17 (P = 0.03), and the variance inflation factor was 1.13. The β value for refractive error was −0.24 (P < 0.01). We thus concluded that myopia had a stronger impact on disc tilt angle than age.

Table 2. Subjects demographics.

| Characteristics of subjects | 187 |
|-----------------------------|-----|
| Number                      | 187 |
| Age (year)                  | 61.4 ± 9.4 |
| Sex (male: female)          | 100 : 87 |
| BCVA (LogMAR)               | −0.07 ± 0.08 |
| Refractive error, SE (D)    | −3.38 ± 3.75 |
| Baseline IOP (mmHg)         | 16.9 ± 4.3 |
| IOP on the test day (mmHg)  | 13.6 ± 2.6 |
| MD (dB)                     | −4.71 ± 3.26 |
| PSD (dB)                    | 8.08 ± 4.18 |
| MD slope (dB/Y)             | −0.12 ± 0.38 |

BCVA: best corrected visual acuity
SE: spherical equivalent, IOP: intraocular pressure
MD: mean deviation, PSD: pattern standard deviation
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Stereoscopic Analysis of Glaucomatous Optic Nerve Head
Table 3. Optic nerve head parameters.

| Parameters                              | mean ±SD   | Parameters                              | mean ±SD   |
|-----------------------------------------|------------|-----------------------------------------|------------|
| Vertical disc width (mm)                | 1.86±0.23  | Rim-disc ratio of section 1             | 0.07±0.05  |
| Horizontal disc width (mm)              | 1.66±0.28  | Rim-disc ratio of section 2             | 0.11±0.06  |
| Vertical cup-disc ratio                 | 0.82±0.08  | Rim-disc ratio of section 3             | 0.17±0.06  |
| Horizontal cup-disc ratio               | 0.74±0.08  | Rim-disc ratio of section 4             | 0.20±0.08  |
| Minimum rim-disc ratio                  | 0.02±0.02  | Rim-disc ratio of section 5             | 0.15±0.08  |
| Angle of minimum rim-disc ratio (degree)| 187.4±127.0| Rim-disc ratio of section 6             | 0.06±0.05  |
| Superior minimum rim-disc ratio         | 0.08±0.06  | Cup volume (mm³)                        | 0.31±0.22  |
| Angle of superior minimum rim-disc ratio(degree) | 72.9±18.7 | Disc volume (mm³)                       | 0.93±0.43  |
| Inferior minimum rim-disc ratio         | 0.04±0.05  | Rim volume (mm³)                        | 0.17±0.10  |
| Angle of inferior minimum rim-disc ratio (degree) | 284.1±14.9 | Mean cup depth (mm)                     | 0.20±0.09  |
| Disc aspect ratio                       | 1.14±0.18  | Maximum cup depth (mm)                  | 0.52±0.19  |
| Cup aspect ratio                        | 1.28±0.24  | Height variation contour (mm)            | 0.58±0.26  |
| Superior rim width (mm)                 | 0.21±0.10  | Maximum depth value of the depth map (mm)| 0.85±0.28 |
| Inferior rim width (mm)                 | 0.12±0.09  | Minimum depth value of the depth map (mm)| −0.14±0.25|
| Cup area (mm²)                           | 1.45±0.57  | Rim category                            | 5.77±0.95  |
| Disc area (mm²)                         | 2.42±0.63  | DDLS stage                              | 3.77±0.95  |
| Rim area (mm²)                          | 0.97±0.27  | Rim decentering                         | 0.30±0.42  |
| Cup-disc area ratio                     | 0.58±0.11  | Disc tilt angle (degree)                | 10.5±12.5  |
| Rim-disc area ratio                     | 0.42±0.11  | Rim decentering (absolute value)        | 0.44±0.27  |

SD: standard deviation

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Table 4. Correlation between optic nerve head parameters and glaucoma patient data.

| Parameters                              | Age (year) | BCVA (LogMAR) | Spherical equivalent refractive error (D) | Pretreatment IOP (mmHg) | IOP on the test day (mmHg) | MD (dB) | PSD (dB) | MD slope (dB/y) |
|-----------------------------------------|------------|---------------|------------------------------------------|------------------------|-----------------------------|---------|----------|-----------------|
|                                         | r          | P value       | r                                        | P value                | r                           | P value | r        | P value         |
| Vertical disc width                     | -0.180     | 0.014 *       | 0.205                                    | 0.736                  | -0.137                       | 0.061 * | 0.132    | 0.072           |
| Horizontal disc width                  | 0.072      | 0.330         | 0.087                                    | 0.236                  | 0.145                       | 0.047 * | 0.081    | 0.268           |
| Vertical cup-disc ratio                | 0.130      | 0.076         | 0.209                                    | 0.689                  | -0.027                       | 0.713   | 0.246    | 0.001           |
| Horizontal cup-disc ratio              | 0.103      | 0.160         | 0.100                                    | 0.173                  | 0.052                       | 0.481   | 0.199    | 0.006           |
| Minimum rim-disc ratio                 | -0.111     | 0.129         | -0.045                                   | 0.539                  | 0.082                       | 0.266   | -0.157   | 0.032           |
| Superior minimum rim-disc ratio        | 0.072      | 0.330         | 0.075                                    | 0.310                  | 0.240                       | 0.001 * | -0.099   | 0.176           |
| Angle of superior minimum rim-disc ratio| 0.062      | 0.396         | -0.004                                   | 0.955                  | 0.210                       | 0.004 * | 0.039    | 0.594           |
| Inferior minimum rim-disc ratio        | -0.154     | 0.035 *       | -0.046                                   | 0.530                  | -0.007                       | 0.929   | -0.154   | 0.035           |
| Angle of inferior minimum rim-disc ratio| -0.133     | 0.070         | 0.006                                    | 0.939                  | -0.253                       | 0.000 **| -0.043   | 0.557           |
| Disc aspect ratio                      | -0.310     | 0.000 **      | -0.154                                   | 0.036                  | -0.330                       | 0.000 **| 0.014    | 0.852           |
| Cup aspect ratio                       | -0.242     | 0.001 **      | -0.162                                   | 0.027                  | -0.313                       | 0.000 **| -0.003   | 0.969           |
| Superior rim width                     | -0.029     | 0.695         | 0.075                                    | 0.311                  | 0.104                       | 0.158   | -0.115   | 0.177           |
| Inferior rim width                     | -0.285     | 0.000 **      | -0.107                                   | 0.144                  | -0.199                       | 0.006 **| -0.146   | 0.047           |
| Cup area                               | 0.089      | 0.226         | 0.114                                    | 0.120                  | 0.080                       | 0.276   | 0.188    | 0.010           |
| Disc area                              | -0.003     | 0.967         | 0.077                                    | 0.294                  | 0.075                       | 0.310   | 0.115    | 0.117           |
| Rim area                               | -0.134     | 0.068         | 0.004                                    | 0.962                  | 0.030                       | 0.686   | -0.129   | 0.080           |
| Cup-disc area ratio                    | 0.159      | 0.030 *       | 0.114                                    | 0.121                  | 0.070                       | 0.340   | 0.248    | 0.001           |
| Rim-disc area ratio                    | -0.160     | 0.029 *       | -0.114                                   | 0.122                  | -0.073                       | 0.324   | -0.246   | 0.001           |
| Rim-disc ratio of section 1            | 0.097      | 0.186         | -0.073                                   | 0.323                  | 0.379                       | 0.000 **| -0.232   | 0.001           |
| Rim-disc ratio of section 2            | 0.002      | 0.980         | 0.023                                    | 0.758                  | 0.185                       | 0.011 * | -0.150   | 0.040           |
| Rim-disc ratio of section 3            | -0.235     | 0.001 **      | -0.074                                   | 0.317                  | -0.198                       | 0.007 **| -0.158   | 0.031           |
| Rim-disc ratio of section 4            | -0.177     | 0.016 *       | -0.074                                   | 0.314                  | -0.314                       | 0.000 **| -0.091   | 0.216           |
| Rim-disc ratio of section 5            | -0.230     | 0.002 **      | -0.109                                   | 0.139                  | -0.299                       | 0.000 **| -0.115   | 0.117           |
| Rim-disc ratio of section 6            | -0.164     | 0.025 *       | -0.151                                   | 0.039                  | -0.064                       | 0.385   | -0.175   | 0.016           |
| Cup volume                             | 0.087      | 0.237         | 0.079                                    | 0.284                  | 0.232                       | 0.001 **| 0.123    | 0.093           |
| Disc volume                            | -0.176     | 0.016 *       | -0.167                                   | 0.022                  | 0.027                       | 0.715   | 0.186    | 0.011           |
| Rim volume                             | -0.338     | 0.000 **      | -0.137                                   | 0.062                  | -0.257                       | 0.000 **| -0.046   | 0.534           |
| Mean cup depth                         | 0.085      | 0.246         | 0.052                                    | 0.479                  | 0.281                       | 0.000 **| 0.072    | 0.328           |
| Maximum cup depth                      | 0.067      | 0.361         | 0.044                                    | 0.547                  | 0.237                       | 0.001 **| 0.056    | 0.444           |
| Height variation contour               | -0.215     | 0.003 **      | 0.015                                    | 0.834                  | -0.433                       | 0.000 **| 0.091    | 0.215           |
| Depthmap maximum                       | -0.141     | 0.055         | -0.156                                   | 0.033                  | -0.001                       | 0.987   | 0.107    | 0.145           |
| Depthmap minimum                       | -0.141     | 0.055         | -0.156                                   | 0.033                  | -0.001                       | 0.987   | 0.107    | 0.145           |
Table 4. Cont.

| Parameters                  | Age (year) | BCVA (LogMAR) | Spherical equivalent refractive error (D) | Pretreatment IOP (mmHg) | IOP on the test day (mmHg) | MD (dB) | PSD (dB) | MD slope (dB/y) |
|-----------------------------|------------|---------------|----------------------------------------|------------------------|---------------------------|---------|----------|-----------------|
|                             | r          | P value       | r                                      | P value                | r                         | P value | r        | P value         |
| Rim category                | 0.048      | 0.514         | 0.049                                  | 0.509                  | -0.121                    | 0.100   | -0.024   | 0.741           | -0.626         | 0.000         | **       | 0.213           | 0.003         | **       | -0.011          | 0.880         |
| DDLS stage                  | 0.048      | 0.514         | 0.049                                  | 0.509                  | -0.121                    | 0.100   | -0.024   | 0.741           | -0.626         | 0.000         | **       | 0.213           | 0.003         | **       | -0.011          | 0.880         |
| Rim decentering             | 0.118      | 0.106         | 0.123                                  | 0.094                  | 0.160                     | 0.029   | 0.088    | 0.232           | -0.017         | 0.822         | *        | -0.018          | 0.305         | *        | -0.027          | 0.717         |
| Disc tilt angle             | -0.300     | 0.000         | **                                    | -0.183                 | *                         | -0.361  | 0.026    | 0.719           | -0.069         | 0.351         | **       | -0.035          | 0.630         | 0.068    | 0.356           | 0.005         | 0.964         |
| Rim decentering (absolute value) | 0.140     | 0.056         | 0.128                                  | 0.081                  | 0.163                     | 0.026   | 0.073    | 0.318           | -0.101         | 0.168         | 0.142   | 0.053           | -0.080         | 0.277    |

Spearman’s rank correlation coefficient: *; P value <0.05, **; P value <0.01, r: correlation coefficient

BCVA: best corrected visual acuity, IOP: intraocular pressure, MD: mean deviation, PSD: pattern standard deviation.
of the ONH, multiple approaches to investigate ONH morphology are needed.

To obtain results reflecting the nature of this morphology, we devised two novel measurement parameters. Rim decentering, one of the new parameters, was calculated with a formula that determined the difference in the rim ratio between the superior and inferior areas. The resulting data suggested that this ratio might help classify eyes with the FI disc type and identify regionally damaged areas in glaucomatous eyes. Seventy-five percent of patients in this study had a positive value for rim decentering, suggesting that the inferior rim of the ONH was more vulnerable to glaucomatous change than the superior. Furthermore, the angle of the inferior minimum rim disc ratio was 284 degrees, which was consistent with rim damage being more common in the inferotemporal disc region [39,40].

The other new measurement parameter used in this study was the tilt angle of the disc. We found that the group of glaucoma patients included in our study showed characteristically steeply sloping ONHs, with an average tilt of 10.5 degrees and a tilt of more than 30 degrees in seven percent of patients. Existing studies use varying definitions of disc tilt. Tay et al. used the index of tilt, which was calculated as the quotient of the minimum diameter of the disc divided by its maximum. They defined ONHs as significantly tilted when they had an index of tilt less than or equal to 0.80 [41]. However, other studies have set 0.70 or 0.75 as the criterion for significant tilt [42,43]. These previous methods of determining tilted discs relied on alternative measurement indices, but 3D photographs are capable of providing a direct value for tilt angle and can help in judging the severity of deformity. We found that tilt angle was moderately correlated to refractive error and age, and a multivariate analysis revealed that refractive error was a stronger indicator of a tilted disc than age. In Asia, the prevalence of myopia is significantly higher than in Western countries [44]. Previous studies have reported that myopia and elongated axial length were associated with a higher prevalence of glaucoma [45–49]. Morphologically, an elongated axial length laterally stretches the choroid and retina. As a result, the ONH tends to develop a myopic type tilted disc with crescent peripapillary atrophy. As our data did not include axial length, our analysis of myopic glaucomatous factors used refractive error, which is correlated with axial length. Nevertheless, we believe that quantification of disc tilt with the nonmyd WX may be able to identify a heightened risk of glaucoma in patients, and form a useful future part of clinical analyses of the ONH.

The stereo fundus camera technique used in this study had limits that may have affected our results. In a few patients, structures such as peripapillary atrophy can reduce the color contrast of Eslanchig’s scleral ring, rendering the image fuzzy and creating difficulties in determining the contour line of the disc edge. Nevertheless, even in such cases, a stereoscopic image provides more information than a monoscopic image, and should lead to more accurate prognoses. This study was also limited by being hospital-based and retrospective, although it included a relatively high number of patients.

In conclusion, we determined baseline ONH data with a simultaneous stereo fundus camera and identified a number of factors, including vertical C/D ratio, rim width and rim area, which were associated with glaucoma severity in the early and middle stages of the disease. Additionally, we found that tilted discs were correlated to spherical equivalent refractive error. We believe that quantitative data on ONH morphology is a powerful tool for clinical research into glaucoma.

Supporting Information

Figure S1 Schemata of measurements for the area and volume of the cup, disc and rim. The reference plane was defined as the average height of the cup contour. The zero-mm plane was defined as the average height of the nasal retinal surface outside the disc area. Contour lines for the disc and cup were based on observer-determined points on the fundus photograph (typically 8–14,) with computer-generated spline interpolation used to generate the final curve. The area and volume of the cup, disc and rim were determined with these two contour lines and the two planes, as illustrated. The superior and the inferior rim widths were measured on the vertical axis of the optic nerve head. In the cup area, the maximum depth and the mean depth were calculated. The height variation contour was calculated by subtracting the minimum height of the disc contour line from its maximum height. Maximum height and minimum height of the depth map were defined as the maximum height and minimum height of the measurement area.

(TIF)

Figure S2 Schema of the aspect ratio. The aspect ratio was calculated by dividing the length of the largest diameter (the major axis) of the optic disc by the perpendicular diameter (the minor axis).

(TIF)

Figure S3 Illustration of rim sections and rim decentering. a) Definitions of the superior and inferior sections of the rim area. The superior section for measurements ranged from 60° to 120° and the inferior section ranged from 240° to 300°. These sections were used to calculate the minimum rim-to-disc ratio and its angle. b) Definitions of the six sections of the rim area. The six sections of the rim were defined as follows: section 1 ranged from 0° to 45° and from 315° to 360°, section 2 ranged from 45° to 90°, section 3 ranged from 90° to 135°, section 4 ranged from 135° to 225°, section 5 ranged from 225° to 270°, and section 6 ranged from 270° to 315°. These six sections were used to calculate the average of the sectional minimum rim-to-disc ratios. Rim decentering was determined with the following formula: rim decentering = (superotemporal rim area [2] − inferotemporal rim area [6])/((superotemporal rim area [2] + inferotemporal rim area [6])).

(TIF)

Figure S4 Definition of disc tilt angle. The disc tilt angle was defined as the degree of the angle between the plane horizontal to the observer and the line between 0° and 180° on the disc edge. T: Temporal, N: Nasal, θ: disc tilt angle.

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Author Contributions

Conceived and designed the experiments: T.Nakagawa KN MK YK T.Nakazawa. Performed the experiments: YY MT KN MK YK KO ST T.Nakazawa. Analyzed the data: YY MT. Contributed reagents/materials/analysis tools: T.Nakagawa. Wrote the paper: YY MT T.Nakagawa T.Nakazawa.
References

1. Quigley HA (1996) Number of people with glaucoma worldwide. Br J Ophthalmol 80: 389–393.
2. Resnikoff S, Pascolini D, Etya’ale D, Kocur I, Pararajasegaram R, et al. (2004) Global impact on visual impairment in the year 2002. Bull World Health Organ 82: 844–851.
3. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Kelner JL, et al. (2002) The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 120: 701–713; discussion 829–730.
4. Martus P, Streoux A, Buddle MM, Mardin CY, Korth M, et al. (2005) Predictive factors for progressive optic nerve damage in various types of chronic open-angle glaucoma. Am J Ophthalmol 139: 999–1009.
5. Tezel G, Siegmund KD, Trinkaus K, Wax MB, Kass MA, et al. (2001) Clinical factors associated with progression of glaucomatous optic disc damage in treated patients. Arch Ophthalmol 119: 813–818.
6. Johnson CA, Kelner JL, Krohn MA, Porney GL (1979) Photogrammetry of the optic disc in glaucoma and ocular hypertension with simultaneous stereo photography. Invest Ophthalmol Vis Sci 18: 1252–1263.
7. Robin AL, Quigley HA, Pollock IP, Maumenee AE, Maumenee IH (1979) An analysis of visual acuity, visual fields, and disk cupping in childhood glaucoma. Am J Ophthalmol 87: 847–858.
8. Francis NR, Varma R, Vigen C, Lai MY, Winarto J, et al. (2011) Population and high-risk group screening for glaucoma: the Los Angeles Latino Eye Study. Invest Ophthalmol Vis Sci 52: 6257–6264.
9. Lloyd MJ, Mansberger SL, Fortune BA, Nguyen H, Torres R, et al. (2013) Features of optic disc progression in patients with ocular hypertension and early glaucoma. J Glaucoma 22: 343–348.
10. Nakazawa T, Shimura M, Ryu M, Himori N, Nitta F, et al. (2012) Progression of visual field defects in eyes with different optic disc appearances in patients with normal tension glaucoma. J Glaucoma 21: 426–430.
11. Nicolela MT, Drance SM (1996) Various glaucomatous optic nerve appearances: clinical correlations. Ophthalmology 103: 640–649.
12. Park HY, Lee K, Park CK (2012) Optic disc torsion direction predicts the location of glaucomatous damage in normal-tension glaucoma patients with myopia. Ophthalmology 119: 1844–1853.
13. Wolfs RC, Ramrattan RS, Hofman A, de Jong PT (1999) Cup-to-disc ratio: ophthalmoscopy versus automated measurement in a general population: The Rotterdam Study. Ophthalmology 106: 1597–1601.
14. Asakawa K, Kato S, Shirakashi M, Yaoeda K, Funaki S, Funaki H, et al. (2004) Optic disc topography as measured by a confocal scanning laser ophthalmoscope and visual field loss in Japanese patients with primary open-angle or normal-tension glaucoma. J Glaucoma 13: 291–298.
15. Parkin B, Shuttlesworth G, Coston M, Davison C (2001) A comparison of stereoscopic and monoscopic evaluation of optic disc topography using a digital optic disc stereoview camera. Br J Ophthalmol 85: 1347–1351.
16. Girkin CA, McGwin G, Jr., McNeal SF, DeLeon-Ortega J (2003) Racial differences in the association between optic disc topography and early glaucoma. Invest Ophthalmol Vis Sci 44: 3382–3387.
17. Zangwill LM, Weinreb RN, Berry CC, Smith AR, Dirkes KA, et al. (2004) Racial differences in optic disc topography: baseline results from the confocal scanning laser ophthalmoscopy ancillary study to the ocular hypertension treatment study. Arch Ophthalmol 122: 22–28.
18. Jayaundera T, Danesh-Meyer HV, Donaldson M, Gamble G (2005) Agreement between stereoscopic photographs, clinical assessment, Heidelberg retina tomograph and digital stereoscopic optic disc camera in estimating vertical cup:disc ratio. Clinical and Experimental Ophthalmology 33: 259–263.
19. Onodaka K, Nakazawa T, Ootomo T, Nakamura M, Fuse N, et al. (2010) Correlation between morphology of optic disc determined by Heidelberg Retina Tomograph II and visual function in eyes with open-angle glaucoma. Clin Ophthalmol 4: 763–773.
20. Garway-Heath DF, Hitchings RA (1998) Quantitative evaluation of the optic nerve head in early glaucoma. Br J Ophthalmol 82: 352–361.
21. Jonas JB, Fernandez MC, Sturmer J (1993) Pattern of glaucomatous neuroretinal rim loss. Ophthalmology 100: 63–68.
22. Tay E, Seah SK, Chan SP, Lim AT, Chew SJ, et al. (2005) Optic disc ovoidity as an index of tilt and its relationship to myopia and perimetry. Am J Ophthalmol 139: 247–252.
23. You QS, Xu L, Jonas JB (2006) Tilted optic discs: The Beijing Eye Study. Eye 20: 270–279.
24. How AC, Tan GS, Chan YH, Wong TT, Seah SK, et al. (2009) Population prevalence of tilted and torted optic discs among an adult Chinese population in Singapore: the Tanjong Pagar Study. Arch Ophthalmol 127: 894–898.
25. Sawada A, Tomidokoro A, Azoe M, Iwasue A, Yamamoto T (2008) Refractive errors in an elderly Japanese population: The Cajima study. Ophthalmology 115: 363–370 e363.
26. Mitchell P, Horiuchi F, Sandbach J, Wang JJ (1999) The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology 106: 2010–2015.
27. Ghiadh K, Heijl A, Bengtsson B (2001) Refractive error and glaucoma. Acta ophthalmologica Scandinavica 79: 560–566.
28. Perera SA, Wong TY, Tay SY, Cheung JP, Saw SM, et al. (2010) Refractive error, axial dimensions, and primary open-angle glaucoma: the Singapore Malay Eye Study. Arch Ophthalmol 128: 900–905.
29. Xu L, Wang Y, Wang S, Jonas JB (2007) High myopia and glaucoma susceptibility in the Beijing Eye Study. Ophthalmology 114: 216–220.
30. Suzuki Y, Iwasue A, Azoe M, Yamamoto T, Abe H, et al. (2006) Risk factors for open-angle glaucoma in a Japanese population: the Tajima Study. Ophthalmology 113: 1613–1617.