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Optic Disk Size and Glaucoma

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Abstract

Assessment of optic disk size is an important, but often overlooked, component of the diagnostic evaluation for glaucoma. Measured values of optic disk size vary with the measurement technique utilized. Available methods for disk size measurement and their respective strengths and limitations will be discussed. Further, actual disk size varies with race and possibly other demographic characteristics. Disk size is also associated with variation of specific anatomical structures of the optic nerve head and the retinal nerve fiber layer. These disk size-dependent variations may influence the susceptibility to glaucoma or the likelihood of glaucoma diagnosis. This manuscript reviews the published evidence relating to disk size and glaucoma.

Keywords

demographics; disk morphology; glaucoma; measurement techniques; optic disk size

I. Introduction

Detection of characteristic glaucomatous optic disk damage involves the measurement of the size and shape of the neuroretinal rim and optic cup. Assessment of optic disk size is an important component of optic nerve examination as the size of the neuroretinal rim and the optic cup vary with disk size. 13,60,75,127 Several factors make the determination of whether disk size is an independent risk factor for glaucoma susceptibility difficult. First, measurement techniques can provide different estimates of disk size, limiting comparison among studies. 2,4,8,9,13,19,31,42,91,102,103,122,156,158,167,168,182 Second, there is a large variation in disk size within a population and also among populations. 11,72,86,93,100,103,106,125,126,128,146,154 Third, disk size itself may influence the likelihood that a clinician makes a diagnosis of glaucoma, thus providing a potential source of bias. 8,37 It is often easier to detect a glaucomatous appearing optic nerve head if the disk is large compared to one that is small. If disk size is in fact an independent risk factor for the development of glaucoma, it is relevant to consider the anatomical features that are responsible for the increased susceptibility.

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This review addresses the impact of measurement technique and population characteristics on reported optic disk size. In addition, the influence of disk size on the appearance of the optic disk and nerve fiber layer and how this may relate to glaucoma susceptibility is discussed.

II. Techniques for Measuring Disk Size

The estimate of optic disk size is dependent on the instrument and method used for measurement. 1,2,4,5,13,17,52,58,102,122,131,137,138,165,167,171,182 Systematic measurement error may occur depending on the instrument and technique used. The size of an optic disk image is dependent on instrument magnification and the magnification properties of the eye. Corneal curvature, axial length, and ametropia may all affect the latter. Direct measurement of the optic disk size is only possible during vitreoretinal surgery or histologically. 52 Therefore, several correction factors have been developed to correct for the camera magnification and eye magnification error. 5,16,122,123 The advantages and limitations of each method are shown in Table 1 and are outlined below.

A. HISTOMORPHOMETRY

Histomorphometry of histological preparations is an invaluable research tool for assessing structural features of the optic disk. This type of evaluation is complicated, time-consuming, expensive, and has been performed only by a few researchers. 94,100,149,150,188 Disk size estimates are dependent on the histological techniques used, and results may differ amongst different research groups. Mean disk size measurements using histomorphometric techniques in normal eyes range from 2.57 mm² to 2.81 mm². 142,149,152 Further limitations are the cost and availability of eyes, the changes in the tissue postmortem, the fixation method, and the specialized equipment required. The major advantage of this direct measurement method is its independence from magnification correction error.

B. SLIT-LAMP BIOMICROSCOPY

Slit-lamp biomicroscopy is an easy, rapid, and inexpensive method for estimating the size of the optic disk. 2,4,158,168 Using this measurement technique, the average disk area and vertical disk diameter are easily estimated using different handheld high power convex lenses (e.g., +60 D, +78 D, Superfield NC, or +90 D) and an adjustable vertical beam height on the slit-lamp. The development of several lens-specific correction factors allows estimation of the size of the optic disk. 52,102 Slit-lamp biomicroscopic measurements of the optic disk show an acceptable intra- and interobserver variability (coefficient of variation using a 78-D lens: 2.45 %, interobserver differences in mean disk diameter measurements using a 60-D lens: – 0.04 mm). 58,168 Examination of the optic disk without pupil dilation reads to significantly poorer interobserver agreement compared to dilated pupils (Vertical disk diameter measurement: 95% limits of agreement 0.2404 without dilation and 0.1607 with dilation, P=0.0125).¹¹³

A limitation of using indirect lenses is that the distance from the lens to the eye may vary and influence the accuracy of the magnification correction, particularly in the presence of a high refractive error. In addition, Ansari and colleagues 4 showed that a single magnification correction factor for each lens is not appropriate. The reason for this inaccuracy is that under myopic conditions, fundus lenses underestimate the true size of the examined object, while hyperopia leads to an overestimation.^{4,5} Therefore, Ansari and colleagues calculated individual fundus lens correction factors p (°/mm) for several fundus lenses. The total change in magnification over a range of ametropia (–12.5 D to + 12.6 D) was highest for the +60-D fundus lens, compared to the +78-D, + 66-D stereo fundus lens, +90-D, and Superfield NC lens (Table 2). High-magnification minimizes the depth of the field and should reduce errors in the measurement.

C. PLANIMETRY

Planimetry provides quantitative optic disk measurements by plotting disk stereophotographs on paper and measuring them manually or with the help of computerized techniques. 29,30, 32,156,169,171 Both, Jonas 102 and the investigators of the Blue Mountains Eye Study 136 demonstrated good inter- and intra-observer agreement for experienced observers using planimetry (Interobserver intraclass correlation coefficient was reported to be 0.91 for disk area measurements in the Blue Mountains Study). Mean disk area measurements in the normal white population using planimetry range from 1.70 mm² to 2.89 mm².49,59,88

There are several limitations to the use of planimetry for measuring disk size. It is a time-consuming technique, and also depends upon the subjective judgment of the edge of the optic disk. In general, the use of refraction to correct for magnification is less accurate than the use of axial length and can lead to biased estimates of disk size. 52 Using spherical error as the correction factor may underestimate the size of the disk in large eyes and overestimate the size of the disk in small eyes. 52

D. IMAGING

Confocal scanning laser ophthalmoscopy (CSLO) provides rapid, objective and highly reproducible measurements of optic disk size. The average disk area measured with CSLO in normal Caucasian subjects ranges from 1.74 mm² to 2.47 mm². 21,70,96,177,184 The Heidelberg Retina Tomograph (HRT, Heidelberg Engineering, Heidelberg, Germany) employs a 670 nm diode laser to sequentially scan the retinal surface in the x and y directions at multiple focal planes. Using confocal scanning principles, a three-dimensional topographic image is constructed from a series of optical image sections at consecutive focal planes. 115 With the current version of the HRT II software (version 1.7.0.2) an operator outlines the optic disk margin, and topographic measurements, including disk area are calculated automatically. The recently released software (software version 3.0) includes the provision of topographic measurements that does not require the outlining of the disk margin. Magnification is corrected using keratometry and refraction. Advantages of CSLO imaging include the reduced need for dilated pupils and clear media, and the automated analyses available. The images are acquired rapidly and easily. Limitations include the reliance on an operator to define the optic disk margin and for some topographic optic disk parameters a reference plane to identify the plane of measurement.

The optical coherence tomograph (Stratus OCT, Carl Zeiss Meditec, Dublin, California) also has been used to assess optic disk topography in clinical practice. This instrument provides in-vivo cross sectional scans of retinal structures by the use of low-coherence interferometry. 68,130,162,163 The optic nerve head scan consists of six radial scans in a spoke like pattern centered on the optic nerve head. The OCT interpolates between the scans to provide measurements throughout the optic nerve head. OCT provides an automated demarcation of the disk margin as the end of the retinal pigment epithelium/choriocapillaris layer. The demarcation can be manually adjusted in cases where the software does not appropriately determine the border of the retinal pigment epithelium. The average disk area measurement in the normal white population using the OCT ranges from 2.10 mm² – 2.35 mm². 130,164, 185 The OCT has further been shown to provide reproducible assessment of optic disk topography and retinal nerve fiber layer. 162,163 The transverse scan size (circle diameter or line length) displayed for StratusOCT is determined assuming zero refractive correction and average axial eye length. If these conditions are not true for the eye being scanned, the scan size at the retina will be different than the value shown. StratusOCT does not adjust scan size to compensate for refractive error or axial length. The normative data limits for retinal and RNFL thickness reflects the range of refractive corrections and axial lengths for the population used to determine these limits (personal communication Thomas Will, Carl Zeiss Meditec,

Jena, Germany, January 2006). Advantages of the OCT include the automated determination of the disk margin and the automated analysis of topographic parameters and retinal nerve fiber layer thickness. Limitations include the need to interpolate between six radial scans to obtain topographic measurements, the need for pupil dilation in some eyes and to adjust the automated disk margin in selected eyes. In addition, for some subjects pupil dilation is necessary to obtain good quality scans.

E. COMPARISON OF DISK AREA ESTIMATES USING DIFFERENT MEASUREMENT TECHNIQUES

Although disk area measurements obtained using various techniques are generally strongly correlated, the absolute disk size measurement may differ considerably. Larger disk size estimates have been reported using planimetry compared to a Goldmann three-mirror contact lens (Horizontal mean disk diameter $1.77 \text{ mm} \pm 0.24 \text{ mm}$ vs. $1.39 \text{ mm} \pm 0.22 \text{ mm}$).^{102, 168} However, using a +90 D fundus lens, Ruben and colleagues found good agreement between planimetry and biomicroscopic disk size estimates.¹⁵⁸ Jonas and associates found that planimetric measurements of disk size were larger compared to CSLO measurements in a mixed group ($n = 432$) of healthy subjects, patients with ocular hypertension and glaucoma patients. (Planimetry: $2.79 \text{ mm}^2 \pm 0.66 \text{ mm}^2$ vs. CSLO $2.56 \text{ mm}^2 \pm 0.63 \text{ mm}^2$).⁹⁶ These discrepancies may be due to differences in the correction of the image magnification,^{5,16, 17,52,123} misalignment between patient and fundus camera or CSLO,^{6,143,145} and a different outlining of the optic disk boundaries.^{144,170} In contrast, Garway-Heath et al reported no difference in optic disk size estimates between planimetric and CSLO measurements in healthy subjects (Planimetry: $1.97 \text{ mm}^2 \pm 0.36 \text{ mm}^2$ vs. CSLO: $1.98 \text{ mm}^2 \pm 0.35 \text{ mm}^2$, $n = 88$).⁵³ Correlation between disk size estimates using the CLSO and +60-D, +78-D, and +90-D funduscopy lenses is reported to be moderate to good (correlation coefficients range from 0.59–0.80).¹²¹ OCT topographic optic disk measurements are well correlated with CSLO measurements.^{66,130,164} However, in one study OCT measurements of disk area tend to be larger than that of the CSLO ($2.15 \text{ mm}^2 \pm 0.36 \text{ mm}^2$ vs. $1.85 \text{ mm}^2 \pm 0.30 \text{ mm}^2$, normal subjects).¹⁶⁴ Another study found no statistically significant difference between the CSLO and Stratus OCT disk area measurements.⁶⁶

F. SUMMARY OF MEASUREMENT TECHNIQUE

Various techniques are available for estimating optic disk size. Each has specific strengths and limitations when applied to certain types of clinical and research objectives. Some of the measurement techniques are more applicable to clinical practice than others. The levels of skill required to obtain good quality information can vary by technique. It is important to understand that these various techniques provide different estimates of disk size, which should be taken into consideration when comparing disk size measurements among different patient populations.

III. Patient Factors That Influence Disk Size

A. RACE

1. Race and Disk Size—African-Americans have larger disks than individuals from other races. However, using a variety of methods, estimates of the mean disk area in African-Americans range from 2.14 mm^2 to 3.75 mm^2 ,^{125,181} compared with 1.73 mm^2 to 2.63 mm^2 in Caucasians,^{35,51,54,55,110,125,177,181,191} and 2.46 mm^2 to 2.67 mm^2 in Hispanics,¹⁷⁷ and 2.47 mm^2 to 3.22 mm^2 in Asians.¹²⁵ (Table 3). Larger optic disks in African-Americans have also been shown in normal,^{35,54,55,125,126,191} post-mortem,¹⁴⁹ and glaucomatous^{54,128} eyes, including evidence from population-based studies.¹⁸¹ Population-based studies provide non-selected samples and have larger numbers of

participants. Therefore, the possibility of selection bias is reduced, providing more representative and robust estimates of disk size in the population.

From the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study (OHTS), Zangwill and colleagues 191 found that African-Americans have significantly larger optic disks ($2.17 \text{ mm}^2 \pm 0.41 \text{ mm}^2$) than other racial groups ($1.87 \text{ mm}^2 \pm 0.38 \text{ mm}^2$). African-Americans further had larger cup area and larger neuroretinal rim area than the other participants. However, after adjusting for optic disk area, these differences between the African-American race and other racial groups were no longer statistically significant. Therefore, differences in topographic parameters between the African-American race and other groups can be largely explained by larger optic disk areas in the African-American population. This study emphasizes the importance of considering disk size when assessing the neuroretinal rim and optic cup in glaucoma management decisions. 37, 51,61,75,110

2. Race, Disk Size, and Glaucoma Susceptibility

The high prevalence of glaucoma in individuals of certain African and African-Caribbean populations (2.8% 157 to 8.8% 129) combined with the presence of larger optic disks compared to the Caucasian population 35,55,125,126,153,181 has led to the hypothesis that large optic disks might be more prone to glaucomatous damage than small disks. 28 The Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the OHTS evaluated the hypothesis that large disks may be an important predictor of POAG in OHTS participants. However, disk size was not associated with the development of POAG in OHTS participants. 190 Jonas also reported that susceptibility to glaucoma was independent of disk size in white patients. 83

Recent evidence from the OHTS further suggests that the increased risk conferred by African-American race may be accounted for by other variables measured in the study. Higginbotham and colleagues 64 reported that after adjusting for baseline cup/disk ratio, age, sex, central corneal thickness, systemic diseases, and IOP in the OHTS, African-American race was not associated with a statistically significant increased risk of developing POAG when applying multivariate statistics. 56,64 It is likely therefore, that various factors may explain the higher rates of glaucoma in African-Americans. These may include genetic susceptibility to POAG, 45 higher prevalence of comorbidity, such as cardiovascular disease, diabetes and systemic hypertension, 63,108,173 or thin corneas. 62,116,141

B. SEX

1. Sex and Disk Size—Several studies have evaluated the influence of gender on optic disk size (Table 4). 1,21,181,192 Using the CSLO, Bowd and colleagues demonstrated that optic disk area did not differ significantly between males and females ($P > 0.05$). 21 This was supported by several other studies that measured disk size using confocal scanning laser ophthalmoscopes. 1,42,109

In studies that have reported differences in disk size between genders, the differences were small. Population-based studies with a large number of subjects, such as the Baltimore Eye Survey 153,181 tended to report significantly larger disks in males compared to females. The Baltimore Eye Survey 181 examined a population-based sample of black and white Americans in their race, age-, sex-, and refractive error related differences in optic disk topography using the Topcon Image Analyzer. This survey found significantly larger disk areas in male compared to female subjects. Despite the statistically significant sex differences, the difference was not very large [mean disk area (95% CI) Caucasian females vs. Caucasian males: 2.60 mm^2 (2.57–2.63 mm^2) vs. 2.66 mm^2 (2.62–2.70 mm^2), respectively].

2. Sex and Glaucoma Susceptibility—Reports on the role of sex as a risk factor for glaucoma, are inconclusive. The Blue Mountains Eye Study, 136 the Baltimore Eye Survey, the Beaver Dam Eye Study 114 and the Los Angeles Latino Eye Study 180 found no association between sex and the prevalence of glaucoma. However, the Barbados Eye Study 69,118 reported a higher prevalence of glaucoma in men (13.3%) than women (8.5%) and reported that male sex was a risk factor for glaucoma in their predominantly black study population. In contrast, the Blue Mountains Eye Study reported a higher prevalence of glaucoma in women in each age group, with a borderline significance after adjusting for age (odds ratio 1.55; CI 1.03–2.32) using logistic regression.

Although there might be small differences in disk size between females and males, no studies have directly evaluated whether sex and disk size influences the susceptibility of glaucoma.

C. AGE

1. Age and Disk Size—Age does not appear to be associated with disk size in humans. 1, 21,22,53,99,110,181 This evidence is supported by population-based studies including the Baltimore Eye Survey, 181 the Rotterdam Study, 155 and the Reykjavik Eye Study.⁴³ In the Baltimore Eye Survey, a moderate to high percentage of older subjects was excluded due to poor quality stereophotographs or unreliable analyses. The following percentages (according to five age groups) were excluded: 40–49 years: 15.6%, 50–59 years: 21.0%, 60–69 years: 29.9%, 70–79 years: 48.5%, and 80+ years: 78.9%. Therefore, the results of the relationship between age and disk size have to be interpreted with caution. One cross-sectional population-based study from Bengtsson and colleagues 14 found a small increase in optic disk diameter with age in a population of 1,287 subjects in Sweden. However, the increase in disk diameter of approximately 0.001 mm per year was very small. Others suggested that the slight increase in disk size with age might be artefactual 7 and related to the method used for magnification correction. 53 Histological evaluations by Cavallotti 33,34 also found an age-related increase in optic disk size in the rat and human optic nerve head, respectively. However, one has to bear in mind that cross-sectional studies are susceptible to cohort effects. Therefore, longitudinal studies are needed to investigate aging effects on disk size.

2. Age and Glaucoma Susceptibility—There is, however, a strong relationship between increasing age and glaucoma. The prevalence of glaucoma does increase with age from about 1% at the age of 50 years to about 4% at the age of 80 years. 114 The age-specific prevalence rates are comparable in the large population-based studies, ranging from 1.2 % to 1.4% in subjects under 65 years old 107,114,136 to 2.0% to 8.7% in subjects of 70 – 85 years old. 39,107,114,136,174 No evidence for a relationship between age, disk size and glaucoma susceptibility has been reported yet.

D. MYOPIA

1. Myopia, Disk size, and Glaucoma Susceptibility—Myopic eyes may show larger and more elongated optic disks than emmetropic eyes, especially eyes with high myopia > –8D. 1,92 However, in a range of –5D to +5D of refractive error, optic disk size is not associated with refractive error. 76,104,159 The enlargement of the optic disk size is explained, in part, by a stretching of the disk and therefore, a deformation of the lamina cribrosa. One might hypothesize that the deformation of the lamina cribrosa in highly myopic eyes is similar to alterations and thinning of the lamina cribrosa in glaucoma. 94,152 How this deformation in myopic eyes influences the risk for developing glaucoma is still unclear, although Jonas and associates 78 suggested higher glaucoma susceptibility in highly myopic eyes (–8 D) with large optic disks compared to non-highly myopic eyes. Population – based studies including the Blue Mountains Eye Study 135 and the Barbados Eye Study 186 found a strong relationship between myopia and glaucoma. The Blue Mountains Eye Study reported prevalences that ranged from

1.5% in emmetropes to 4.4% in moderate to high myopes. 135 The Barbados Eye Study found that myopia (worse than −5 diopters) increased the odds of having glaucoma while hyperopia reduces the odds of having glaucoma (1.48 (1.12, 1.95, 95% CI versus 0.52 (0.41, 0.67, 95% CI) in black participants. Hospital-based studies, which are subject to selection bias, report results for 57,118,135 and against 81,98,151 an increased prevalence of glaucoma in myopic patients.

E. NORMAL-TENSION GLAUCOMA

1. Normal-tension Glaucoma and Disk Size—Many attempts have been made to investigate possible differences in optic disk size in subjects with Normal Tension Glaucoma (NTG), POAG and in non glaucomatous eyes. 28,176,178,187 The size of the optic nerve head has been reported to be either similar 44,71,77,134,140 or larger 28,72,112,178 in patients with NTG compared to POAG (Table 5). Although there may be different patterns of optic disk cupping and disk size in NTG, there is wide variability of the definition of NTG. 46,117,119, 175 More than a century ago, Donders 40 already proposed that all cases of NTG are misclassified POAG. The reason for the misclassification was reported to be a failure to detect the abnormal intraocular pressure peaks. Some studies define NTG based on some degree of diurnal IOP testing while others do not. It is possible that many cases of apparent NTG (in non-Japanese individuals) are misclassified POAG, because the existence of abnormal high intraocular pressure peaks was not ruled out with certainty in these NTG patients.

Moreover, selection bias may influence the results of many non population – based studies. For example, the chance of diagnosing a patient with NTG may be higher in patients with a large disk than a small disk. The larger the disk and the cup/disk ratio, the higher is the likelihood that glaucoma is diagnosed. Similarly, small glaucomatous disks may have lower cup/disk ratios and may be underdiagnosed, providing a further source for bias. 72,80 The population – based Blue Mountains Eye Study found that mean disk diameter was similar between OAG and NTG patients using planimetric measurement techniques. 59 More population – based studies are needed to evaluate the relationship between disk size and various types of glaucoma. Table 5 presents an overview of studies that compare optic disk size in various types of glaucoma and healthy eyes.

F. OCULAR HYPERTENSION

1. Ocular Hypertension and Disk Size—Jonas and colleagues have evaluated a large number of patients with ocular hypertension (n= 265 eyes) and compared the optic disk size in these patients to patients with primary open-angle glaucoma (n=274 eyes), normal-pressure glaucoma (n= 193 eyes), and secondary open-angle glaucoma (n=31 eyes) using planimetry. 99 They found no difference in disk size among the groups. This is in concordance with a previous report from Iester et al, who measured disk size of healthy individuals (n= 62), ocular hypertensives (n= 182), and patients with primary open-angle glaucoma (n= 182) using CSLO. 70 The results of the Blue Mountains Eye Study on the other hand showed that ocular hypertensive eyes (n= 254) had significantly smaller disks than patients with primary open angle glaucoma (n= 184), 59 but the difference was small (POAG mean vertical disk diameter: 1.56 mm ± 0.2 mm vs. OHT mean vertical disk diameter 1.49 ± 0.18 mm, Table 5).

G. ANGLE-CLOSURE GLAUCOMA

1. Angle-closure Glaucoma and Disk Size—The prevalence of angle-closure glaucoma varies considerably depending on the population studied. Estimates range from 0.1% in the Caucasian population 15,67 to 2% – 5% in Eskimos. 3,36,41 According to Sihota, disk size measured with OCT is smaller in angle-closure glaucoma patients compared to primary open-angle glaucoma patients is smaller (2.57 mm 2 ± 0.4 mm 2 vs. 2.85 mm 2 ± 0.3 mm 2,

respectively). 166 More studies comparing optic disk size among angle-closure glaucoma and other types of glaucoma are warranted.

H. SUMMARY OF PATIENT FACTORS

There is consistent and strong evidence that black individuals have larger disks compared to white individuals. Disk size is significantly, but only slightly larger in males than in females in some studies. Selection bias must be considered when interpreting the relationship between the type of glaucoma and disk size in non population-based studies.

IV. The Effect of Disk Size on Optic Disk Morphology

A. DISK SIZE, NEURORETINAL RIM AREA AND RETINAL NERVE FIBER LAYER (RNFL)

The number of retinal nerve fibers in healthy eyes varies between individuals and ranges from 750,000 to 1,500,000 million.^{100,103,111} The intrapapillary retinal nerve fibers form the neuroretinal rim. There is consistent evidence, regardless of the measurement technique that rim area increases with increasing disk size. ^{21,22,24,31,48,49,79,86,110} This raises the question, as to whether large disks have more optic nerve fibers than small disks. A larger number of nerve fibers may represent a larger anatomical reserve in various optic neuropathies including glaucoma.

Some histologic studies have reported a positive correlation between disk size and the number of nerve fibers, ^{103,150} while other studies have not confirmed this relationship ^{133,188} (Table 6). Specifically, Quigley et al ¹⁵⁰ found that the number of nerve fibers increased linearly with increasing disk size in monkey eyes ($n = 25$). This association was subsequently confirmed by Jonas and colleagues ¹⁰³ who demonstrated that in humans ($n = 72$), larger disks have more nerve fibers compared to small disks. However, conflicting data were reported by Mikelberg and colleagues. ¹³³ In their study, there was no correlation between the optic nerve fiber count and disk size in humans ($n = 16$). In laser-induced glaucoma of 10 monkey eyes, Yucel et al ¹⁸⁸ also did not find a correlation between the number of nerve fibers and the disk area measured with a confocal scanning laser ophthalmoscope (Heidelberg Retina Tomograph). Another study from Savini and colleagues found a positive correlation between optic disk size and 360° retinal nerve fiber layer thickness both measured by optical coherence tomography ($r = 0.50$, $P = 0.0001$). ¹⁶⁰ Funaki and coworkers investigated the relationship between the size of the optic disk and retinal nerve fiber layer thickness as measured by scanning laser polarimetry in 60 healthy eyes. They found a positive correlation ($r = 0.497$, $P > 0.0001$) between optic disk size and the integral of peripapillary retinal thickness. ⁴⁷ These contradictory results among studies may be explained at least in part by differences in the methodology used for estimating disk size (histological vs. imaging technique), differences in histomorphologic technique, species (animal vs. human) and the number of eyes examined.

B. DISK SIZE AND CUP/DISK RATIO

There is large variation in cup disk ratios within any given population. Jonas and colleagues have performed several groundbreaking studies on morphometry of the optic nerve head and the importance of considering disk size in glaucoma diagnosis. ^{23,74,105} According to Jonas, cup/disk ratio can range from 0.0 to 0.9 in the healthy population, ⁹¹ and there is considerable overlap between normal and glaucomatous eyes. The vertical cup/disk ratio is positively associated with optic disk size in normal and glaucomatous eyes. ^{22,37,51,75,91} The Blue Mountains Eye Study ³⁷ (6,678 eyes) showed a positive relationship between cup/disk ratio and disk size. In this population-based sample the median cup/disk ratio increased from 0.35 to 0.55 from small (1.1 – 1.3 mm) to large (1.8 – 2.0 mm) disk diameter with a linear increase in median and 95th percentiles values in vertical disk diameter (Fig. 1).

The importance of assessing cup/disk ratio corrected for disk size has been extensively studied by Jonas and coworkers. ⁷⁶ They showed for example, that the vertical cup/disk ratio corrected for disk size had the highest diagnostic power compared to other optic disk parameters for separating normal subjects from preperimetric glaucoma patients. ⁷⁵

Although cup/disk ratio measurements can be easily performed by most ophthalmologists and do not require additional imaging equipment, the single measurement has limited value in the estimation of glaucomatous damage if not adjusted for disk size. ³⁷ This is, because the relationship between disk size and cup/disk area ratio is important since a large cup/disk ratio can be physiologic in a large disk, while an average cup/disk ratio may be present in a small disk with glaucoma. A tendency for overdiagnosis in large disks and underdiagnosis in small disks is therefore possible.

Nevertheless, the estimation of the vertical cup/disk ratio is one of the most frequently performed clinical methods for a simple assessment of the optic disk in glaucoma diagnosis and follow-up. ^{22,37,51} Table 6 presents differences in optic disk morphology in relation to disk size.

Estimation of the disk size is also important in diagnosing diseases other than glaucoma as some optic nerve anomalies such as optic disk drusen, pseudopapilledema, optic nerve hypoplasia, or anterior ischemic optic neuropathy occur preferentially in small optic disks, ^{73,85,87,89,139} while other conditions, such as morning glory syndrome and optic disk pits are more common in large disks. ^{80,95,101}

C. DISK SIZE AND LAMINA CRIBROSA

The lamina cribrosa pores represent the canals through which the optic nerve axons travel from the retina to the brain. Lamina pores have been evaluated in several recent clinical and histopathological studies. ^{18,124,161,172} The largest pores of a healthy human optic nerve head are arranged in a vertical hourglass distribution, with more pores and larger pores at the inferior and superior poles. ¹⁴⁸ Some studies found less connective tissue at the poles, indicating less structural support for the nerve fibers passing through. ^{38,142} This may explain the preferential nerve fiber loss in the superior and inferior pole region. Larger disks have a larger total lamina cribrosa area and more lamina pores than small disks, ^{80,97} potentially allowing more space for nerve fibers to travel through and therefore, possibly reducing the likelihood of focal compression to the axons. On the other hand, the pressure differential across the lamina cribrosa could produce an increased deformation and displacement of the central tissue in large disks, leading to greater glaucoma susceptibility in large disks. Burgoyne and co-workers have described the optic nerve head as a biomechanical structure and their paradigm suggests that mechanical failure of the connective tissue of the lamina cribrosa underlies glaucomatous cupping. Therefore, large disks may be more susceptible to pressure damage as per Laplace's law. ^{12,26}

As the influence on disk size on the lamina cribrosa resistance and amount of connective tissue is complex, ^{12,25,26,27,149} further investigation is needed.

D. SUMMARY OF OPTIC DISK MORPHOLOGY

Structural characteristics associated with large disks may include a larger number of nerve fibers, more and larger lamina cribrosa pores, a larger neuroretinal rim area, and a higher cup/disk ratio. As the size of the neuroretinal rim and cup are often used in the differential diagnosis of glaucoma, it is important to estimate disk size so that an accurate assessment can be made (Table 6).

V. Conclusion

The evaluation of disk size is an essential part of optic disk assessment to diagnose and manage glaucoma. It enhances assessment of features of the optic disk, such as neuroretinal rim and cup area, that are necessary for accurate diagnosis and monitoring. It is also important to understand that patient characteristics 28,35,72,125,128,149,178,181 and the method used for measurement 16,50,52,122,131 will influence disk size estimates. Longitudinal studies are needed to evaluate the complex relationship between disk size, neural tissue, clinical and demographic factors and the development of glaucoma. Although few studies have directly addressed this issue, there is no evidence that disk size is an independent risk factor for glaucoma.

VI. Method of Literature Search

Papers and abstracts of relevant studies for this review were obtained from the MEDLINE database. The following search words (inclusive MESH headings) were used: *optic disk AND size AND glaucoma, measurement AND glaucoma, prevalence AND glaucoma, incidence AND glaucoma, race AND glaucoma, gender AND glaucoma, Hispanics AND glaucoma, optical coherence tomography AND glaucoma AND disk size, nerve fiber count AND optic disk, morphometry AND optic nerve head, lamina cribrosa AND optic nerve head*. The search covered the years from 1970 to 2004 and articles published in English and in German were included. Additional sources included publications cited in relevant articles. Criteria for inclusion or exclusion of articles were the originality, the importance for the ophthalmoscopic evaluation of the optic nerve head, and critical judgment of different techniques for evaluation of the optic disk, findings in different groups of glaucoma, and demographic characteristics.

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Graph A**Graph B****Figure 1.**

Graph A shows the influence of vertical disk diameter on the 50th, 95th, 97.5th, and 99th percentiles for vertical cup/disk ratio. Graph B shows the relationship between the vertical cup/disk ratio and the vertical disk diameter after grouping the data into small (1.1 – 1.3 mm), medium (>1.3 – < 1.8 mm) and large (1.8 – 2.0 mm) optic disks. An increase of 0.2 in median vertical cup/disk ratio (0.35 – 0.55) was observed between small and large disks. An equivalent increase of 0.2 (0.59 – 0.74) was observed for the 97.5th percentile from small to large disk (with Permission from the Br J Ophthalmology and the Blue Mountains Eye Study)

Table 1

Advantages and Limitations of different measurement methods

Method	Application	Magnification correction required?	Pupil Dilation required?	Subjective identification of disk margin?	Rapid?	Other limitations	Author
Histomorphometry	Research	No	-	-	No	Post mortem change in tissue, special equipment required	Jonas, 100,103, Quigley, 149 Akman, 2 Ansari, 4 Lichter, 120 Lim, 121
Biomicroscopy	Clinical/ Research	Yes	Yes	Yes	Yes	Subjective, measurements vary with the fundus lens used	Montgomery, 137,138 Ruben, 158 Jonas, 72,74,80, 82,91,96 Miller, 134 Mitchell, 136 Peigne, 147 Varma, 179
Planimetry	Research	Yes	Yes	Yes	No	Subjective	Garway-Heath 52 Britton, 10 Bottoni, 20,167 Garway-Heath 49 Tomita 176 Tuulonen 178 Agarwal, 1 Bathija, 10 Bowd, 21 Burk, 28,29 Hoffmann, 65 Lester, 70,71 Kiriyama, 112 Medeiros, 130 Spencer, 167 Weinreb, 183 Zangwill, 189, 191 Wollstein 184 Hoffmann, 65 Medeiros, 130 Schuman, 162, 163,164 Wollstein 185
Computerized Planimetry	Research	Yes	Yes	Yes	No		
Confocal Scanning Laser Ophthalmoscopy (CSLO)	Clinical/ Research	Yes	No	Yes	Yes	Measurements based on reference plane	
Optical Coherence Tomography (OCT)	Clinical/ Research	Yes	No/Yes	No	Yes	Interpolation between scans	
ILM: Inner limiting membrane, RPE: retinal pigment epithelium							

Correction factors p determined by Ansari and colleagues 4,5 for high power funduscopy lenses and change in total magnification over a wide range of ametropia

Table 2

Lens	Volk +60 D	Volk +78 D	Volk +90 D	Volk Superfield NC	Volk +66 D Stereo
Correction factor p					
Total magnification change from myopia (−12.5 D) to hyperopia (+12.6 D)	3.04 (0.04)* −21.1% to +24.0%	3.69 (0.06)** −13.2% to +13.9%	4.64 (0.02)** −15.1% to +13.7%	4.61 (0.03)** −13.3% to +14.0%	3.56 (0.06)** −12.9% to +16.2%

* Correction factor constant over a range of refraction from −12.5 D to + 12.6 D

** Correction factor constant over a range of refraction from −5 D to + 5 D

Values are given in mean (SD)

Table 3

Race and Disk Size

Author	Subjects (n)	Race	Diagnostic Groups	Design	Parameter	Method	Correction	Results
Chi 1989 35	N (61)	Black (30) White (31)	Normals	Cross- Sectional Cohort study	MDA	Rodenstock Optic Disk Analyzer	N/A	MDA Blacks 2.15 (0.056) vs. Whites 1.73 (0.061), P<0.0001
Zangwill 2004 191	OHT (451)	White (337) Black (75) Hispanic (25)	OHT	Other OHTS Ancillary Study	MDA	HRT I	Keratometry and ametropia	MDA Blacks 2.17 (0.41) vs. Whites 1.87 (0.38), P<0.001
Mansour 1992 126	N (66) Children	Black (30) White (36)	Normals	Cross-sectional	MDA	Stereophotographs	N/A	MDA Blacks 3.08 (0.55) vs. Whites 2.66 (0.54), P<0.002
Varma 1994 181	N (4877)	Black (1534) White (1853) Black (43) White (44) Asian (45)	Normals	Population-based study	MDA	Topcon Optic Disk Analyzer	Littmann	MDA Blacks 2.94 (0.74) vs. Whites 2.63 (0.46), P =0.0001
Tsai 1995 177	N (132)	White (51) Black (21) Hispanic (24) Indian (15) Oriental (14)	Normals	Cross-sectional	MDA	HRT I	Keratometry and ametropia	MDA Blacks 2.67 (0.44) vs. Whites 2.40 (0.28) p=0.011
Mansour 1991 125	N (125)	White (68) Black (84)	Normals	Cross-sectional	MDA	Stereophotographs	Littmann	MDA Blacks 3.33 (0.12) vs. Whites 2.66 (0.11) P N/A
Girkin 2003 54	N (150)	White (63) Blacks (86)	Normals	Cross- Sectional Cohort study	MDA	HRT II	Keratometry and ametropia	MDA Blacks 2.26 (0.45) vs. Whites 1.98
Girkin 2003 54	N (149)	Black (73) White (53)	Glaucoma	Cross- Sectional Cohort study	MDA	HRT II	Keratometry and ametropia	MDA Blacks 2.45 (0.60) vs. Whites 2.24 (0.40) P N/A
Girkin 2005 55	N (126)		Normals	Cross- Sectional Cohort study	MDA	HRT II	Keratometry and ametropia	MDA Blacks right eye 2.14 (0.05) vs.

Author	Subjects (n)	Race	Diagnostic Groups	Design	Parameter	Method	Correction	Results
								Whites 1.96 (0.06) P=0.01 MDA Blacks left eye 2.18 (0.05) vs. Whites 2.02 (0.06) P=0.04

MDA (SD): Mean disk area, OHT: Ocular Hypertension, N: Normal, N/A.: not available, NS: not significant, Correction: Magnification Correction

Table 4

Sex and Disk Size

Author	Method of measurement	Females		Males		Statistical significance
		Subjects (n)	Disk area mm ² (SD)	Subjects (n)	Disk area mm ² (SD)	
Baltimore Eye Survey, Varma 1994 181	Topcon Image Analyzer	1992 (white)	2.60 (0.47)*	1483 (white)	2.66 (0.55)*	Yes (p<0.03)
Baltimore Eye Survey, Varma 1994 181	Topcon Image Analyzer	854 (black)	2.91 (0.61)*	1049 (black)	3.00 (0.57)*	Yes (p<0.005)
Britton 1987 22	computerized planimetry	69	2.10 (0.5), m+f	44	2.10 (0.5), m+f	No (p>0.05)
Mansour 1991 125	Zeiss Funduscamera	57	2.89 (0.56)	68	3.09 (0.57)	Yes (p<0.04)
Mansour 1992 126	Zeiss Funduscamera	18 (white)	2.57 (0.49)	18 (white)	2.74 (0.59)	No (p>0.05)
Mansour 1992 126	Zeiss Funduscamera	16 (black)	3.05 (0.54)	14 (black)	3.11 (0.56)	No (p>0.05)
Mislior 1994 132	computer-aided morphometry	144	2.43 (0.55)	91	2.58 (0.59)	Yes (p<0.05)
Kashiwagi 2000 109	Confocal Scanning Laser Tomograph (TopSS)	48	2.63 (0.48)	44	2.75 (0.47)	No (p>0.2)
OHTS Zangwill 2004 191	HRT I	260	1.90 (0.39)	191	1.96 (0.41)	No (p=1.27)
Durukan 2004 42	HRT II	298	2.12 (0.41)	245	2.11 (0.43)	No (p=0.58)
Bowd 2002 21	HRT I	93	1.80 (0.36)	45	1.78 (0.38)	No (p=0.74)

The standard deviation was not provided in the study by Varma, therefore, we adopted the calculation from Meyer and colleagues 131

M+F: male and female, HRT: Heidelberg Retina Tomograph

Table 5
Comparison of glaucoma types and optic disk size measured by different methods

Author	Subjects (n)	Race	Design	Parameters	Method	Correction	Results
Tuulonen 1992 178	POAG (61) NTG (50) PEX (54)	White	Retrospective	MDA	Computer-assisted Planimetry	N/A	MDA NTG 2.33 (0.48) vs. OAG 2.07 (0.43) vs. PEX 1.94 (0.3) p<0.001
Jonas 1992 72	POAG (549) PEX (78) NTG (22) N (561)	White	Cross-sectional	MDA	Planimetry	Littmann	MDA NTG 2.96 (0.73) > N 2.69 (0.69) > POAG 2.63 (0.61) > PEX 2.53 (0.51) P<0.05
Burk 1992 28	Mixed (148)	White	Prospective	MDA	Scanning Laser Tomography	Keratometry and ametropia	MDA NTG 2.28 (0.58) vs HTG 2.01 (0.46) p<0.0003
Jonas 2000 77	NTG (52) Juvenile OAG (28)	White	Cross-sectional	MDA	Planimetry	Littmann	MDA NTG 2.9 (0.46) vs. MDA juvenile OAG 2.63 (0.63) P=0.11
Healey 1999 59	POAG (106) OHT (135) PEX (81) N (3320)	White	Population-based	MVDD	Planimetry	Refraction	MVDD POAG 1.56 (0.20) > MVDD OHT 1.49 (0.17), PEX 1.50 (0.2), N 1.50 (0.18) P<0.05
Jonas 1998 82	PG (62) POAG (566)	White	prospective	MDA	Planimetry	Littmann	MDA PG 2.67 (0.79) and MDA POAG 2.69 (0.62) NS
Iester 1999 71	NTG (50) HTG (132)	N/A	Cross-sectional	MDA	HRT	Keratometry and ametropia	MDA HTG 2.33 (0.62) vs. NTG 2.33 (0.89), NS
Jonas 1988 90	OAG (233) N (253)	white	Retrospective cross-sectional	MDA	Planimetry	Littmann	MDA OAG 2.57 (0.60) vs. N 2.64 (0.80), NS
Kiriyaama 2003 112	POAG (17) NTG (23) OHT (15)	N/A	Prospective	MDA	HRT	Keratometry and ametropia	MDA POAG 2.23 (0.53) vs. NTG 2.33 (0.48) vs. OHT 2.31 (0.46) NS

Data are presented as Mean (SD) unless otherwise indicated

Correction: Correction for magnification

NTG: Normal Tension Glaucoma, **POAG:** Primary Open Angle Glaucoma, **OAG:** Open Angle Glaucoma, **PEX:** Pseudo-Exfoliative Glaucoma, **PG:** Pigmentary Glaucoma, **HTG:** High Tension Glaucoma, **OHT:** Ocular Hypertension, **N:** Normal

N/A: Not available, **NS:** not significant

MDA: Mean disk area

MVDD: Mean vertical disk diameter

MHDD: Mean Horizontal disk diameter

Table 6**Optic Disc Characteristics: Morphology**

MORPHOLOGY	Method	Sample Size (n)	Results
Number of Nerve fibers	Histology (human) 103	72	Positive correlation with disk size
	Histology (monkey) 150	25	Positive correlation with disk size
	Histology (human) 133	16	Independent from disk size
	Histology (monkey) 188	10	
RNFL density	Histology (human) 103	72	Negative correlation with disk size
	Histology (monkey) 150	25	Independent from disk size
Size of Neuroretinal rim	Optical Imaging 184	131	Positive correlation with disk size
	Optical Imaging 31	38	
	Planimetry 86	234	
	Planimetry 91	457	
	Computerized Planimetry 22	113	
	Optical Imaging 48	194	
	Optical Imaging 21	155	
	Planimetry 24	193	
	Planimetry 49	139	
Cup Disk Ratio	Computerized Planimetry 51	200	Positive correlation with disk size
	Planimetry 91	319	
	Planimetry 37	6678	
Number of Lamina Cribrosa Pores	Histology (human) 97	40	Positive correlation with disk size
Number of Photoreceptors	Histology (human) 146	46	Positive correlation with disk size
Number of cilioretinal arteries	Stereophoto 84	163	Positive correlation with disk size