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ORIGINAL ARTICLE

OPTIC DISC CHARACTERISTICS ASSESSED BY EVALUATION OF CLINICAL OPTIC DISC PHOTOGRAPHS IN GLAUCOMA PATIENTS

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Abstract Purpose: To describe optic disc characteristics assessed by evaluation of clinical optic disc photographs and to utilize these findings to differentiate glaucoma patients and normal subjects.
Patients and Methods: A total of 329 eyes of 329 glaucoma patients and 220 eyes of 220 normal subjects were included. The disc diameter to disc-to-macula distance ratio (DD/DM ratio), cup-to-disc diameter ratio (C/D ratio), disc hemorrhage (DH), and nerve fiber layer defect (NFLD) were quantitatively measured on photography.
Results: The horizontal and vertical DD/DM ratios and C/D ratios were significantly larger in glaucoma patients than those in normal subjects ($P<0.05$, $P<0.0001$). An increase in horizontal and vertical C/D ratios with increasing DD/DM ratio was observed in both groups, but the regression lines were steeper in normal subjects than that in glaucoma patients. Disc hemorrhages (3.3%) and NFLD (37.1%) were seen in glaucoma patients in contrast to none in normal subjects ($P<0.0001$).
Conclusions: Paying attention to three factors -C/D ratio relative to disc size, DH and NFLD- may be a clinically easy method to distinguish glaucoma patients from normal subjects by fundus photograph.
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Key words: cup-to-disc diameter ratio; disc-to-macula distance; disc diameter to disc-to-macula distance ratio; nerve fiber layer defect; disc hemorrhage.

原 著

眼底写真による緑内障患者の視神経乳頭の特徴について

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抄録 目的：緑内障患者と緑内障を有さない正常者の視神経乳頭所見の特徴を臨床眼底写真を用いて評価し，両者の鑑別を試みる．
対象と方法：対象は緑内障患者329例および緑内障を有さない正常者220例の片眼である．眼底写真上で，乳頭径と乳頭黄斑距離との比(DD/DM比)，陥凹乳頭径比(C/D比)，乳頭出血(DH)および網膜神経線維層欠損(NFLD)の有無を評価し比較した．
結果：DD/DM比およびC/D比はともに，正常者に比べて緑内障患者で有意に大きかった．両者でDD/DM比の増加に伴うC/D比の増加がみられた．しかし，DD/DM比とC/D比の一次回帰式の傾きは正常者で有意に大きかった．DHとNFLDは緑内障患者でのみみられた．
結論：本研究から，乳頭径を考慮したC/D比，DHおよびNFLDの評価は，緑内障患者と緑内障を有さない正常者を眼底写真上で見分ける簡易法となり得ることが示唆された．
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キーワード: 陥凹乳頭径比; 乳頭黄斑距離; 乳頭径と乳頭黄斑距離との比; 網膜神経線維層欠損; 乳頭出血.

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Introduction

Glaucoma is clinically characterized by elevated intraocular pressure (IOP), glaucomatous optic atrophy and progressive loss of the visual field[1]. However, a recent study revealed that elevated IOP is not always required for diagnosis of glaucoma because there are many glaucoma patients with normal range of IOPs. In fact, in Japan, normal-tension glaucoma (NTG) is the most common type of chronic open-angle glaucoma[2]. Therefore, examination of optic nerve head and visual field testing has been considered more important than tonometry for detecting and diagnosing glaucomatous optic atrophy.

Several efforts have been utilized recently to reduce the rising cost of medical care. In addition to general medical examination including chest X-ray, total blood count, blood chemistry, urinalysis for early detection of illness in Japan, examination of fundus photograph without mydriasis has been widely performed for detecting glaucomatous optic atrophy in over 30-year-old people based upon the significantly increased population of glaucoma patients in a recent glaucoma survey. In terms of optic nerve head examination, it has been suggested that disc cupping, neural rim, disc hemorrhage (DH), peripapillary atrophy are important for glaucoma diagnosis. However, it is well known that the optic nerve head has wide range of normal variations[3], and normal variations in the physiologic cup, the neural rim, and the peripapillary atrophy may be confused with the changes of glaucoma. Thus, for the purpose of initial screening of glaucomatous optic disc, simple and reliable criteria are needed.

Here, the purpose of the present study is to describe optic disc characteristics assessed by evaluation of clinical optic disc photographs and to utilize these findings to differentiate glaucoma patients and normal subjects in Japan.

Materials and Methods

The studies were performed in accordance with our institution's guidelines and the Declaration of Helsinki on Biomedical Research Involving Human Subjects and protocols were approved by the institution's Committee for the Protection of Human Subjects.

Subjects: All glaucoma patients (total 329 patients) who regularly visited the glaucoma clinic in Hirosaki University Hospital for more than one year and 220 normal control subjects who receive medical examination annually in Shichinohe Hospital were enrolled in this study (Table 1). Each glaucoma patient was carefully followed in our glaucoma clinic consecutively and underwent ophthalmologic examinations including slit lamp examinations, gonioscopic examinations, fundus examinations and visual field tests.

Table 1 Clinical characteristics of glaucoma patients and normal subjects

	Glaucoma patients (n = 329)	Normal subjects (n = 220)
Age (means ± SD years)	64.03 ± 12.83	65.46 ± 8.50
Sex (Female/Male)	189/140	114/106
POAG	190	
NTG	139	

All data represent persons.
POAG; primary open-angle glaucoma, NTG; normal tension glaucoma.

The subjects of the study included 140 males and 189 females with ages ranging from 29 to 88 years, with a mean age of 64.7 ± 10.9 (mean ± SD) years. They were divided according to diagnostic condition into 190 patients with primary open-angle glaucoma (POAG) and 139-patients with NTG. The diagnostic criteria for NTG were as follows: 1) the presence of normal open iridocorneal angles, 2) no evidence of IOP higher than 21 mmHg, 3) glaucomatous changes in visual fields and optic nerve cupping, and 4) the absence of alternative causes of optic neuropathy as determined by magnetic resonance (MR) imaging and fluorescein fundus photography. For the diagnosis of POAG, the criteria were identical with that of NTG except IOP had to be higher than 21 mmHg[4-6]. In this study, various stages of glaucoma were included but all other posterior segment eye diseases or refractive errors over ±5D were excluded. Qualified normal subjects randomly selected from participants who had routine annual medical examinations at Shichinohe Hospital, with evaluations including total blood count, blood chemistry, urinalysis, IOP measurement, mydriatic fundus photography, best-corrected acuities of 0.7 or better, refractive errors within ±5D, and no history of glaucoma and other ocular diseases. Whenever ocular diseases were suspected, the subjects were thoroughly examined by visual field testing, MR imaging and fluorescein fundus photography. Thereafter, patients having an IOP more than 21 mmHg (by non-contact tonometer), asymmetry in the cup-to-disc ratio between the fellow eye exceeding 0.2, optic nerve abnormality and/or visual field defects were excluded. Normal subjects were 106 males and 114 females with ages ranging from 30 to 86 years, with a mean age of 65.5 ± 8.5 (mean ± SD) years. One eye chosen randomly by using coin (head; right eye, tail; left eye) from each subject was evaluated. Informed consents were obtained from all subjects.

Photography: Subjects' pupils were dilated with 1% tropicamide. Photographs had been taken using the TRC-50X retinal camera at the 35 degree setting (Topcon, Tokyo, Japan). The study required all photographs to be readable and to have sufficient photographic quality to be evaluated. The photographs of glaucoma patients and normal subjects were mixed and then examined in a masked fashion by two experienced observers having more than 15 years experience in the glaucoma clinic (I.O. and H.O.). In preparation for the present study, by comparing corresponding stereoscopic photos from 100 patients and control subjects, we made sure that accurate observation (less than 5% difference) of the cupping border, C/D ratio and NFLD in the fundus photographs were consistently achieved by the two observers. The border of the optic disc was identical with the inner side of the peripapillary scleral ring. The optic cup was defined on the basis of contour and not of pallor. In fact, the bending points of all vessels on the disc were regarded as the margin of the cup. Using these photographs, the horizontal and vertical disc diameter (DD) and cup diameter, and the distance between the center of the disc and the macula (DM) were measured. Figure 1 illustrates these distances schematically. Also the presence of DH and/or nerve fiber layer defect (NFLD) was examined. Since the visivility of nerve fiber layer has been shown to correlate with the width of the neural rim[7], well-outlined, dark wedge-shaped areas in the bright striated pattern of the surrounding healthy nerve fiber layer were regarded as NFLD. Additionally, the horizontal and vertical C/D ratio and disc diameter to disc-

to-macula distance ratio (DD/DM ratio) were estimated using the following formula to elucidate the relationship between the C/D ratio and disc size (Figure 1):

Horizontal (or vertical) C/D
= C1/D1 (or C2/D2)
Horizontal (or vertical) DD/DM
= D1/M (or D2/M)

Assuming that DM is constant, the DD/DM ratio would then depend on DD. Kwok Hei Mok et al.[8] described DM in 14 open-angle glaucoma patients and 88 normal subjects and reported that no significant difference in DM was observed between the two groups. Our present data also revealed no significant difference in DM between glaucoma patients and controls, 34.32±1.63 mm and 34.83±1.46 mm on photographic measurement, respectively. In this study, the DM was used as a scale as comparison of disc size, which is why the DD/DM ratio is chosen instead of the disc size.

Statistical analysis: Significant differences between groups were found using Fisher's exact probability test and Mann-Whitney's U-test with a significance level of $P<0.05$. Linear regression analysis was applied to determine the effect of disc size on the C/D ratio.

Results

As shown in Table 2, both horizontal

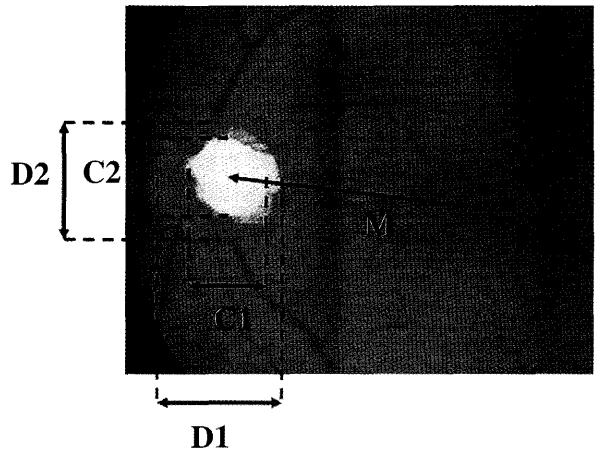

Figure 1 Schematic representation of measurements taken from fundus photographs.
C1 = horizontal cup diameter, C2 = vertical cup diameter, D1 = horizontal disc diameter, D2 = vertical disc diameter, M = distance between center of the optic disc and fovea centralis.

Table 2 Optic disc characteristics of glaucoma patients and normal subjects

	Glaucoma patients (n = 329 eyes)	Normal subjects (n = 220 eyes)
Horizontal DD/DM (range)	0.375 ± 0.052* (0.196 ~ 0.622)	0.367 ± 0.049* (0.265 ~ 0.502)
Vertical DD/DM (range)	0.397 ± 0.040** (0.213 ± 0.526)	0.381 ± 0.046** (0.265 ~ 0.523)
Horizontal C/D (range)	0.707 ± 0.105** (0.335 ~ 0.961)	0.338 ± 0.151** (0 ~ 0.731)
Vertical C/D (range)	0.765 ± 0.111** (0.456 ~ 0.962)	0.342 ± 0.151** (0 ~ 0.663)

All data represent eyes.
Data are means ± SD, unless marked otherwise.
*$P<0.05$, **$P<0.0001$; Mann-Whitney's U-test.

and vertical C/D ratios were much larger in glaucoma patients than normal subjects ($P<0.0001$) as expected. Similarly to this, both horizontal and vertical DD/DM ratios were also significantly larger in glaucoma patients as compared with normal subjects ($P<0.05$, $P<0.0001$, respectively, Table 2). To elucidate the pathophysiological relationship between sizes in discs and cups in glaucoma patients and control subjects, their C/D ratios were plotted against DD/DM ratios. As shown in Figure 2, the vertical C/D ratios increased proportionally with the DD/DM ratios in both groups, but the slopes of their regression lines were different (horizontal data not shown but similar to vertical data). That is, the regression line of normal subjects ($Y=-0.233+1.535X$, $R^2=0.207$, $P<0.005$) (Figure 2a) was much steeper than that in glaucoma patients ($Y=0.507+0.602X$, $R^2=0.049$, $P<0.001$) (Figure 2b). This means that optic disc size should be taken into consideration as a criterion for discriminating between glaucoma disc cups and normal ones. Therefore, we categorized optic disc size variations into three groups as designed by Garway-Heath et al.[9] —small, lower quartile (vertical DD/DM $<$ 0.35); medium, middle quartiles (0.35 $\leqq$ vertical DD/DM $<$ 0.42); large, upper quartile (0.42 $\leqq$ vertical DD/DM) (Table 3) —and C/D ratios in these three groups were compared between glaucoma patients and normal subjects. As shown in Table 4, vertical C/D ratio in all the groups was significantly higher in glaucoma patients as compared with control subjects. However, variations of C/D among the different disc-size groups in normal subjects were much larger than those in glaucoma patients. Therefore, these results clinically indicated that C/D ratios more than 0.68

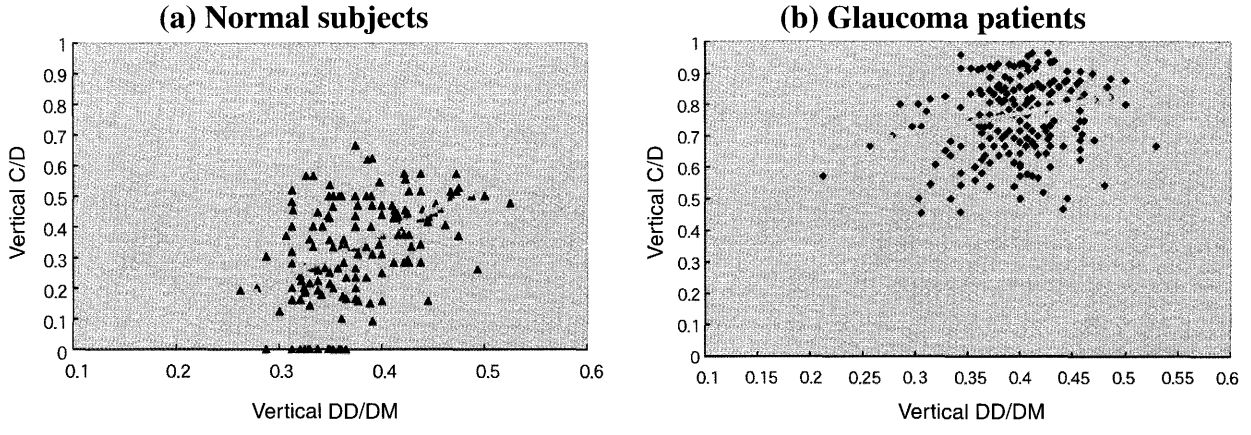

Figure 2 Vertical C/D ratio against vertical DD/DM ratio.
Regression lines of normal subjects and glaucoma patients were shown ($R^2 = 0.207$, $P<0.005$; $R^2 = 0.049$, $P<0.001$, respectively).

Table 3 Three categories of optic disc size variations in normal subjects and glaucoma patients

Vertical DD/DM ratio	Normal subjects (n = 220 eyes)	Glaucoma patients (n = 329 eyes)
$<$ 0.35 (SMALL DISC)	55 (25.0%)	31 (9.4%)
0.35 $\leqq$, $<$ 0.42 (MEDIUM DISC)	110 (50.0%)	194 (59.0%)
0.42 $\leqq$ (LARGE DISC)	55 (25.0%)	104 (31.6%)

All data represent eyes.
DD/DM ratio, disc diameter to disc-to-macula distance ratio.

and less than 0.24 in the small disc group were most likely glaucoma and normal disc, respectively, and glaucoma could not be excluded in discs with a relatively wide range of C/D (0.24-0.68) in this group. In contrast, in medium and large disc size groups, C/D ratios more than 0.77-0.79 and less than 0.37-0.4 were considered as glaucoma and normal disc, respectively, and only a narrow range of C/D ratios (0.4-0.77) remain doubtful about the presence or absence of glaucoma.

As associated disc findings, DH and NFLD were seen in 11 eyes (3.34%) and 122 eyes (37.1%) of glaucoma patients respectively. By contrast, none of them were recognized within normal subjects ($P<0.005$, $P<0.0001$, respectively) (Table 5).

Discussion

It is well known that optic disc changes of glaucoma are characterized by focal or concentric atrophy of the neural rim and enlargement of the cup. However, several glaucoma-like discs such as macro disc with large cupping, developmental disc anomalies such as colobomas, congenital pit, tilted disc syndrome, high myopic disc with large parapapillary atrophy and normal variations of physiological cup and the neural rim may cause confusion of glaucoma diagnosis in the ophthalmology clinic. To lessen the risk of ambiguity, several clinical investigators have proposed clinical parameters to distinguish glaucoma and normal discs. Armaly et al.[10] reported that the vertical and the horizontal C/D ratios were useful for detection of glaucoma and quantification of glaucomatous optic nerve damage. Therefore the C/D ratio has long been used as the clinical indicator to evaluate glaucomatous optic discs. In fact, a number of previous studies revealed that the population of normal subjects with C/D ratio of 0.65 or greater ranged from 2.2% to 4%[11-13], and the incidence of visual field defects increased significantly with C/D ratios greater than 0.7 in ocular hypertensive and glaucoma patients[14]. In the present study, we demonstrated that the horizontal and vertical C/D ratios were significantly larger

Table b Vertical C/D ratios of three disc-size groups in glaucoma patients and normal subjects

	Vertical C/D ratio	
	Glaucoma patients	Normal subjects
SMALL DISC	0.68 ± 0.12**	0.24 ± 0.16**
MEDIUM DISC	0.77 ± 0.12**	0.37 ± 0.14**
LARGE DISC	0.79 ± 0.11**	0.40 ± 0.13**

Data are means ± SD.
C/D ratio, cup-to-disc diameter ratio.
**$P<0.0001$; Mann-Whitney's U-test.

Table F Retinal findings of glaucoma patients and normal subjects

	Glaucoma patients (n = 329 eyes)	Normal subjects (n = 220 eyes)
DH	11 eyes (3.34%)*	0 (0%)*
NFLD	122 eyes (37.1%)**	0 (0%)**

All data represent eyes.
DH, disc hemorrhage; NFLD, nerve fiber layer defect.
*$P<0.005$, **$P<0.0001$; Fisher's exact probability test.

in glaucoma patients than normal subjects ($P<0.0001$). It is well known that the appearances of the optic nerve head and cup generally have vertical and horizontal oval shapes, respectively. Thus horizontal C/D ratios are usually greater than the vertical C/D ratio[11]. Our present study indicated that the difference in C/D ratios between glaucoma patients and control subjects was more significantly evident in the vertical than the horizontal. This corresponds well with the previous observation that the inferior temporal rim in the glaucomatous eye is usually thinner than the superior temporal area, and therefore vertical C/D ratio is much greater than horizontal one in contrast to the normal nerve head[15, 16]. Thus, as an initial screening test, the vertical C/D ratio is thought to be a more useful indicator than the horizontal one for suspecting the presence of glaucomatous optic change.

It's been shown that physiological cup size is significantly influenced by the optic disc size, based upon the fact that the normal population has a wide range of C/D ratio values[3, 17]. In fact, Garway-Heath et al.[9] compared the vertical disc diameter and C/D ratio in normal, early glaucoma and ocular hypertensive subjects, and concluded that the vertical C/D ratio relative to disc size is a useful parameter to assist in identification of glaucomatous discs. However, their method of disc and cup measurements by slit lamp examination is not practical for the initial screening of large numbers of subjects. As a simple estimation of optic disc size, the parameter of DM to DD ratio has been used for the diagnosis of optic disc hypoplasia[18]. Furthermore Mok et al.[8] recently showed that this DM to DD ratio was useful for the identification of macrodiscs. As an additional advantage, this method enables us to compare all photographs with different zoom and by different kinds of fundus camera. We therefore took into account optic disc size estimation by vertical DD/DM ratios for evaluation of whether vertical C/D ratio is physiological or pathological. As shown in Figure 2, plot of vertical C/D ratio against vertical DD/DM ratio revealed that glaucoma patients as well as normal subjects showed an increase in vertical C/D ratio with increasing disc size. However, the regression line in glaucoma patients was much less steep than in normal subjects, suggesting optic disc size should be a critical factor for evaluation of the presence of glaucomatous changes. In the present study, the highest mean value of the vertical C/D ratio of glaucoma patients was 0.79 and the lowest mean value was 0.24 in normal subjects. We therefore propose the following two-step method for detection of glaucoma-suspected optic discs:

- Step1) Vertical C/D ratio lower than 0.24, which is the lowest ratio value among three disc size groups, is most likely physiological; whereas vertical C/D ratio greater than 0.79, which is the largest ratio value among three disc size groups, is most likely glaucomatous, independent of the disc size.
- Step2) When the vertical C/D ratio range is between 0.24 and 0.79, then DD/DM ratio is included in the evaluation as follows:
  1. Large Disc (DD/DM $\geqq$ 0.42), C/D ratio less than 0.4 is most likely physiological and C/D ratio between 0.4-0.79 is suspicious for glaucoma.
  2. Medium Disc (0.35 $\leqq$ DD/DM $<$ 0.42), C/D ratio less than 0.37 is most likely physiological and C/D ratio between 0.37-0.79 is suspicious for glaucoma.
  3. Small Disc (DD/DM $<$ 0.35) are all suspicious for glaucoma.

In the present study, the presence of

DH and NFLD, which are well known to be associated with glaucomatous optic discs, were recognized only in glaucoma patients but not in normal subjects (Table 2). Therefore, in conclusion, a simple assessment of C/D ratio in relation to optic disc size estimation by DD/DM and presence of DH and NFLD are useful methods for detecting glaucoma-suspected discs during annual medical examination. And also we have to examine more glaucoma patients and normal subjects to confirm our methods' utility.

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