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ORIGINAL ARTICLE

Performance of imaging devices versus optic disc and fiber layer photography in a clinical practice guideline for glaucoma diagnosis

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PURPOSE. *To compare the performance of Moorfields Regression Analysis (MRA) and optical coherence tomography (OCT) with that of photographic evaluation of the optic nerve head and retinal nerve fiber layer (RNFL) in the application of the Finnish Evidence-Based Guideline for Open-Angle Glaucoma (FEBG-OAG).*
METHODS. *Patients referred for glaucoma evaluation (n=312) and subjects selected from the general population (n=41) were included in the study. All subjects underwent ophthalmic evaluation, optic nerve head stereophotography, monochromatic RNFL photography, Heidelberg retina tomography, OCT, and laser polarimetry evaluation. The subjects were classified based on stereophotographic or MRA and OCT results by applying the FEBG-OAG.*
RESULTS. *The specificity of the FEBG-OAG for detecting normal patients (stereophotography and imaging devices) was 78% (strict criteria) and 100% (liberal criteria). Agreement between the stereophotographic evaluation and evaluation based on MRA and OCT was 70.2%. Classification of subjects with similar management advice based on these evaluations had 70.5% agreement. Central corneal thickness was a confounding factor in glaucoma diagnosis. Large optic disc sizes played a major role in misleading the diagnosis compared to small discs.*
CONCLUSIONS. *Central corneal thickness and large optic disc size are confounding factors in glaucoma diagnosis. Moorfields Regression Analysis and OCT allow for objective implementation of the FEBG-OAG compared to conventional stereophotographic evaluation of the neuroretinal structures.*

KEY WORDS. *Clinical guidelines, Diagnosis, Glaucoma*

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INTRODUCTION

Open-angle glaucoma is a progressive optic neuropathy characterized by retinal ganglion cell loss and structural changes in the retinal nerve fiber layer (RNFL) and optic nerve head that may lead to visual field (VF) loss (1, 2). Diagnosis of glaucomatous damage is based on the ability of the clinician to detect signs of the disease through clinical evaluation of intraocular pressure (IOP), the appearance of the optic nerve head (ONH) and RNFL, and VF testing. The introduction of imaging techniques, such as laser polarimetry (GDx), Heidelberg retina tomography (HRT), and optical coherence tomography (OCT), offers an objective and quantitative assessment of RNFL and ONH, although no single imaging device outperforms the others. The performance of these tests, however, should be compared to stereophotographic evaluation of the ONH and RNFL by trained observers, as recommended by the Advanced Glaucoma Intervention Study (3).
The major scientific societies have recently presented rec-

ommendations for glaucoma management, such as the European Glaucoma Society Guidelines, the American Academy of Ophthalmology Preferred Practice Patterns for Open-Angle Glaucoma, and the Finnish Evidence-Based Guideline for Open-Angle Glaucoma (FEBG-OAG) (4-6). This latter guideline is based on evaluation of the ONH and RNFL and the recommendations for action are based on very high-quality studies. These guidelines are aimed at providing a uniform diagnosis and treatment of glaucoma by applying evidence-based knowledge to central issues. The ultimate goal of these guidelines is to help clinicians produce effective individual treatment plans for patients with glaucoma (Tab. I).

In the present study, we compared the performance of Moorfields Regression Analysis (MRA) and OCT versus photography for evaluating the ONH and RNFL for application of the FEBG-OAG.

MATERIALS AND METHODS

Subjects

All participants were prospectively enrolled in this study. One eye from each patient was randomly selected for the study. The study protocol was approved by the Aragon Clinical Investigation Ethics Committee (CEICA).

All subjects met the following criteria: age between 30 and 80 years; best-corrected visual acuity of at least 20/30; refractive errors of less than 5 diopters (spherical equivalent) and 3 diopters of astigmatism; open anterior chamber angle; and transparent ocular media. Written informed consent was obtained from all subjects and the study followed the tenets of the Declaration of Helsinki. Exclusion criteria included ocular trauma, surgery, or disease (other than glaucoma); systemic disease with ophthalmic involvement; or inability to perform any procedure of the study.

Procedures

All subjects underwent a full ophthalmic examination, including evaluation by slit-lamp biomicroscopy, measurement of IOP, central corneal ultrasonic pachymetry (DGH Technology, model DGH 500), ONH stereophotography, standard automated perimetry (SAP), Heidelberg Retina Tomograph 3 (HRT3; Heidelberg Engineering, Heidelberg, Germany), laser polarimetry (GDx-VCC), and OCT (Stratus OCT). Short-wavelength automated perimetry (SWAP) was also evaluated in patients classified into certain groups, following the recommendations of the FEBG-OAG.

Study groups

Application of the FEBG-OAG classifies the subjects into several groups, including those with normal findings, and several groups with suspected glaucoma or glaucoma.

Similar to other studies (7, 8), the participants were not selected by applying a gold standard glaucoma test. Because glaucoma cannot be defined outside the context of structure and function, and both structure and function

TABLE I - EXTRACTED FROM THE FINNISH EVIDENCE-BASED GUIDELINE FOR OPEN-ANGLE GLAUCOMA (6)

Normal	Abnormal	Diagnosis	Comments	Procedure
ONH, VF, NFL		Normal findings		Follow-up without treatment (unless IOP >30 mmHg)
VF, NFL	ONH	Suspected glaucoma	Large optic disc?	
VF, ONH	NFL	Preperimetric glaucoma?	SWAP may be abnormal	
ONH, NFL	VF	Suspected glaucoma	Repeat examination Other cause?	
ONH	VF, NFL	Glaucoma	Small optic disc?	Initiate (or consider initiating) treatment
NFL	VF, ONH	Diagnosis other than glaucoma (e.g., neurologic disease)	Very rare in glaucoma	
VF	ONH, NFL	Preperimetric glaucoma	SWAP may be abnormal	
	ONH, VF, NFL	Glaucoma		

IOP = intraocular pressure; NFL = nerve fiber layer; ONH = optic nerve head; SWAP = short-wavelength automated perimetry; VF = visual field.

were being evaluated in this study, the use of a structural or functional gold standard could induce a bias. Nevertheless, adequate representation of normal subjects and glaucoma patients and suspects was ensured by selecting patients from 2 different sources.

Source 1 (reference group) included hospital staff, subjects with low refractive problems, or patients with problems other than glaucoma that would not interfere with the study (e.g., patients seen in the emergency room with irrelevant ocular symptoms). All these subjects met the inclusion criteria and an additional inclusion criterion of an IOP less than 21 mmHg.

Source 2 (study group) included subjects referred by other ophthalmologists for glaucoma evaluation. Our department is the referral hospital for several ophthalmic outpatient facilities and hospitals that do not have ancillary tests available for glaucoma other than SAP.

Application of the FEBG-OAG in participants from the reference group (source 1) and the study group (source 2)

The FEBG-OAG classifies a given subject into 1 of 8 diagnostic categories (Tab. I). In the present study, we applied the FEBG-OAG based on standard photography or on findings from imaging devices.

Clinical application of the FEBG-OAG based on stereophotography

Standard automated perimetry. Perimetries were performed with a Humphrey field analyzer 745, using the 24-2 Swedish interactive threshold algorithm standard strategy. If fixation losses were greater than 20%, or false-positive or false-negative rates were greater than 33% (rates of reliability fixed by the perimeter software), the test was repeated. The second reliable perimetry was used for this study to minimize the learning effect (9). Consistency of the defects was required; otherwise the perimetries were repeated.

Visual field defects were defined by deficits that produced a cluster of 3 or more points with a lower than 5% probability level or a cluster of 2 or more points with a lower than 1% probability level (points could not be located along the periphery or in the blind spot poles) (10), and/or pattern standard deviation with a 5% probability level or lower, and/or glaucoma hemifield test outside normal limits.

Expert evaluation of ONH stereophotographic sets. Glaucomatous defects were defined by the presence of diffuse or focal defects in the neuroretinal rim or optic disc hemorrhages. The sets were evaluated by 2 independent blinded observers. In case of disparity, agreement was achieved by consensus.

Expert evaluation of RNFL red-free fundus photography. The RNFL photographs were evaluated by 2 experts on a different day than the optic disc photographs. Retinal nerve fiber layer defects were defined by the presence of focal or diffuse loss of retinal nerve fiber bundles.

Application of the FEBG-OAG based on imaging devices

Standard automated perimetry. Evaluation of the VF was not a study variable. The same criteria mentioned above were applied.

ONH evaluation by HRT (Moorfields Regression Analysis). Confocal scanning laser ophthalmoscopy with the HRT3 was performed in a standardized manner by one examiner. The HRT provides topographic measures of the ONH derived from 32 optical sections at consecutive focal depth planes. The spherical equivalent refractive error of each eye was adjusted in the dioptric ring of the HRT. Keratometric values were entered into the software (to correct for magnification errors) and topographic images were obtained through dilated pupils. Good-quality images were checked using the image acquisition quality reference. Only scans with an image quality score of acceptable, good, or very good were included in the study. The margins of the optic discs were manually traced by the same glaucoma specialist (while viewing stereophotographs using a stereoscopic viewer). The MRA (11) compares the rim area distribution to a normative database corrected for age. We used a criterion for glaucoma defined by the presence of any sector outside the 95% interval of confidence.

RNFL evaluation by OCT. The Zeiss Stratus OCT 3000 (Carl Zeiss Meditec, Dublin, CA) was used to measure peripapillary RNFL thickness. The RNFL thickness 3.46-mm scan protocol was used to acquire the OCT images. The RNFL thickness average (OU) analysis protocol was used to obtain the variables included in our study. Good-quality scans had to have focused images from the ocular fundus and a centered circular ring around the optic disc. Examinations with a signal-to-noise ratio less than or equal to 30 dB or less than 95% accepted A-scans were retaken.

Peripapillary RNFL thickness parameters included in this study as clinical criteria of glaucomatous damage (12) were mean RNFL thickness (360º) outside the 95% normal confidence limits and one or more RNFL quadrants outside the 95% normal confidence limits.

Statistical analysis

Statistical analyses were calculated using SPSS (version 15.0; SPSS Inc., Chicago, IL) statistical software. The Kolmogorov-Smirnov test was used to check for a normal distribution of the data. Differences between the groups were then tested using Student *t* test.

RESULTS

A total of 41 control subjects (reference group: source 1) and 312 patients (source 2) were included in the study. The descriptive data of these subjects are shown in Table II.

Diagnostic performance of criteria in the sample extracted from the general population (source 1)

Although we did not use a gold standard for glaucoma in our study, we expected that in the reference subjects (source 1) the number of abnormal findings would fall below the expected prevalence of the disease in the general population, particularly because this group of subjects had a normal ophthalmic evaluation. As expected, most of the reference subjects had normal test findings. After application of the FEBG-OAG, the percentage of reference subjects defined as normal by the guideline (specificity) was high (Tab. III).

Diagnostic performance of the FEBG-OAG in the study group (source 2)

A comparative distribution of the subjects of the study group (source 2) with stereophotographic criteria versus the imaging criteria is shown in Table IV. The FEBG-OAG suggests possible sources of error in the different diagnostic groups, e.g., large ONH size. In other cases, a diagnosis of preperimetric glaucoma was confirmed with the SWAP findings, as suggested by the FEBG-OAG. In participants who required SWAP evaluation, defects were defined by deficits that produced a cluster of 4 or more points with a lower than 5% probability or a cluster of 3 or more points with a lower than 1% probability (points should not be located along the periphery or in the blind spot poles) (13). Quantitative data of the ONH and RNFL measured by HRT and OCT are shown in the corresponding Tables (photographic evaluation and imaging devices, Tabs. V and VI). Also, GDx evaluation (parameter nerve fiber indicator [NFI]) allows for comparison of groups tested with an independent device.

DISCUSSION

No single imaging device outperforms others in distinguishing patients with glaucoma from controls (14). There-

TABLE II - CLINICAL DATA OF SUBJECTS INCLUDED IN THE STUDY AND DIFFERENCES BETWEEN THE TWO SOURCES OF PARTICIPANTS

	Source 1: reference group			Source 2: study group		
	No.	Mean	SD	No.	Mean	SD
Visual acuity	41	0.9	0.1	312	0.9	0.1
Age, y	41	58.0	11.2	312	56.5	12.2
IOP, mmHg	41	15.0	2.5	312	23.3[a]	3.2
Pachymetry, μm	41	552.7	33.3	312	564.0	39.6
C/D ratio, biomicroscopy	41	2.8	1.6	312	5.3[a]	2.1
MD	41	–0.9	2.4	312	–1.5	3.5
PSD	41	1.1	1.4	312	1.8[a]	2.4

C/D = cup-to-disc; IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation.
[a] Statistically significant differences ($p<0.05$) between groups.

TABLE III - COMPARATIVE CLASSIFICATION OF REFERENCE SUBJECTS (SOURCE 1, REFERENCE GROUP) AFTER THE APPLICATION OF THE GUIDELINE WITH PHOTOGRAPHS VERSUS IMAGING DEVICES (MRA AND OCT)

Normal findings	Abnormal findings	Photographic evaluation	MRA and OCT
VF, NFL, ONH	—	32	32
VF, NFL	ONH	4	1
VF, ONH	NFL	2	5
VF	NFL, ONH		
NFL, ONH	VF	3	3
NFL	VF, ONH		
ONH	VF, NFL		
—	VF, NFL, ONH		
Total		41	41
Specificity, %		78	78

MRA = Moorfields Regression Analysis; NFL = nerve fiber layer; OCT = optical coherence tomography; ONH = optic nerve head; VF = visual field.

TABLE IV - COMPARATIVE CLASSIFICATION OF SUBJECTS (FROM SOURCE 2) BASED ON FINDINGS OF PHOTOGRAPHIC EVALUATION OF ONH AND NERVE FIBER LAYER VERSUS CLASSIFICATION BASED ON MRA (HRT) AND OCT

			Visual field + MRA + OCT								
		Normal	VF, NFL, ONH	VF, NFL	VF, ONH	VF	NFL, ONH	NFL	ONH	—	
	Normal	**Abnormal**	**—**	ONH	NFL	NFL, ONH	VF	VF, ONH	VF, NFL	VF, NFL, ONH	Total
Visual field + photographic evaluation	VF, NFL, ONH	—	145[a]	9	18	3					175
	VF, NFL	ONH	1	2[a]	1						4
	VF, ONH	NFL	13		1[a]	1					15
	VF	NFL, ONH	7	20	3	21[a]					51
	NFL, ONH	VF					1[a]		4		5
	NFL	VF, ONH									
	ONH	VF, NFL					2		1[a]		3
	—	VF, NFL, ONH					2	9		48[a]	59
		Total	166	31	23	25	5	9	5	48	312

HRT = Heidelberg retina tomography; MRA = Moorfields Regression Analysis; NFL = nerve fiber layer; OCT = optical coherence tomography; ONH = optic nerve head; VF = visual field.
[a] Concordance of diagnostic groups.

fore, the use of evidence-based guidelines that combine several diagnostic devices can improve patient care. This study was designed to test the performance of the FEBG-OAG in reference subjects with no obvious signs of ocular disease (reference group: source 1) and patients sent to our Glaucoma Unit without further discrimination (study group: source 2). Therefore, the difference between groups is based on the origin of the group.

A gold standard for the diagnosis of glaucoma was not used here to avoid biasing our results by using a structural or functional definition of glaucoma. Subjects from source 1 comprised a sample extracted from the general

TABLE V - FINNISH EVIDENCE-BASED GUIDELINE FOR OPEN-ANGLE GLAUCOMA IMPLEMENTED BY PHOTOGRAPHIC EVALUATION OF ONH AND RNFL[a]

Normal	Abnormal	No.	Disc		Pachymetry		MD		PSD		SWAP abnormal, n (%)	NFI (GDx)		Average thickness (OCT)		FSM (HRT)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD
VF, NFL, ONH	—	175	2.1	0.4	572.1	36.4	–0.3	1.0	1.0	0.7	—	17.8	7.8	96.5	11.3	1.0	1.7
VF, NFL	ONH	4	2.3	0.6	578.0	59.9	0.2	0.9	0.5	0.7	—	14.3	6.8	96.3	7.2	–0.4	0.7
VF, ONH	NFL	15	2.2	0.3	600.7[b]	51.2	–0.1	0.8	0.8	0.7	1 (7)	18.7	6.1	98.5	11.5	0.7	1.2
VF	NFL, ONH	51	2.4[b]	0.5	549.6	31.5	–0.6	1.4	1.1	0.7	21 (41)	24.3[b]	11.6	85.6[b]	19.2	–1.2[b]	1.8
NFL, ONH	VF	5	1.5	0.2	557.8	33.7	–1.0	1.3	1.6	1.9	—	24.4[b]	12.3	81.0[b]	10.9	1.6	1.0
NFL	VF, ONH	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	—	0.0	0.0	0.0	0.0	0.0	0.0
ONH	VF, NFL	3	1.9	0.1	558.3	28.5	–2.7	2.5	3.0	0.3	—	17.0	5.3	86.7	9.0	1.0	1.1
—	VF, NFL, ONH	59	2.2	0.4	542.6	37.7	–6.5[b]	5.4	5.2[b]	3.6	—	43.6[b]	22.2	70.8[b]	13.3	–2.6[b]	2.4
Reference group		41	2.0	0.3	552.7	33.3	–0.9	2.4	1.1	1.4	—	14.5	8.4	101.2	10.4	1.6	1.5

HRT = Heidelberg retina tomography; MD = mean deviation; NFL = nerve fiber layer; OCT = optical coherence tomography; ONH = optic nerve head; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer; SWAP = short-wavelength automated perimetry; VF = visual field; FSM = Frederick S. Mikelberg discriminant function; NFI = nerve fiber indicator.
[a] The Table shows the number of subjects in each category and the different functional and structural parameters. Short-wavelength automated perimetry was only performed in the categories recommended by the Finnish Evidence-Based Guideline.
[b] Significant differences versus the reference group ($p<0.05$).

TABLE VI - FINNISH EVIDENCE-BASED GUIDELINE FOR OPEN ANGLE GLAUCOMA IMPLEMENTED BY IMAGING DEVICES (MRA AND OCT)[a]

Normal	Abnormal	No.	Disc		Pachymetry		MD		PSD		SWAP abnormal, n (%)	NFI (GDx)		Average thickness (OCT)		FSM (HRT)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD
VF, NFL, ONH	—	166	2.1	0.4	577.7[b]	38.0	–0.3	1.0	0.9	0.7	—	16.5	6.6	99.1	9.4	1.1	1.5
VF, NFL	ONH	31	2.5[b]	0.4	551.9	27.6	0.3	0.9	0.7	0.7	—	20.5	7.7	95.5	10.2	–1.5[b]	1.2
VF, ONH	NFL	23	2.0	0.3	566.4	33.8	–0.3	1.0	1.1	0.9	5 (22)	24.3[b]	11.3	83.5[b]	11.3	1.2	1.9
VF	NFL, ONH	25	2.3	0.6	544.5	35.9	–1.2	1.3	1.3	0.8	13 (52)	30.8[b]	10.7	77.4[b]	10.8	–1.6[b]	1.7
NFL, ONH	VF	5	1.8	0.3	557.2	26.4	–3.0	3.0	3.6	1.4	—	14.0	0.7	89.2	9.5	0.5	1.2
NFL	VF, ONH	9	2.3	0.4	573.3	45.4	–4.6[b]	6.0	4.5[b]	2.4	—	24.9[b]	12.0	86.4	6.7	–1.0	1.3
ONH	VF, NFL	5	1.6	0.2	556.6	33.1	–0.7	0.6	1.3	1.3	—	26.2[b]	11.0	78.2[b]	6.6	1.6	1.0
—	VF, NFL, ONH	48	2.21	0.41	536.5	34.1	–7.0[b]	5.3	5.4[b]	3.8	—	48.3[b]	21.4	66.2[b]	10.8	–3.0[b]	2.4
Reference group		41	2.0	0.3	552.7	33.3	–0.9	2.4	1.1	1.4	—	14.5	8.4	101.2	10.4	1.6	1.5

HRT = Heidelberg retina tomography; MD = mean deviation; MRA = Moorfields Regression Analysis; NFL = nerve fiber layer; OCT = optical coherence tomography; ONH = optic nerve head; PSD = pattern standard deviation; SWAP = short-wavelength automated perimetry; VF = visual field; FSM = Frederick S. Mikelberg discriminant function; NFI = nerve fiber indicator.
[a] The Table shows the number of subjects in each category and the different functional and structural parameters. Short-wavelength automated perimetry was only performed in the categories recommended by the Finnish Evidence-Based Guideline.
[b] Significant differences versus the reference group ($p<0.05$).

population with similar demographic data (ethnicity, age, visual acuity) than the study group, but without findings in routine ophthalmic evaluation. As in the general population, glaucoma patients may be found in this group, but the prevalence of such cases is expected to be lower than that in the general adult population because routine examination excluded subjects with any evident damage in fundus evaluation. Despite the unlikelihood of finding a glaucoma patient in the reference group, these subjects should not be considered as a "conventional" control group, but rather as a sample that allows for comparison with the general adult population.

Application of the FEBG-OAG classified most of these subjects as normal subjects (without abnormal findings). Therefore, the diagnostic criteria defined for stereophotographic evaluation of the ONH and RNFL and the imaging devices showed high specificity, although the strict sense of specificity must be questioned because a gold standard was not used to verify the diagnosis, which was inherent to the study design. The prevalence of glaucoma in these subjects (without obvious signs of ocular disease) is expected to be lower than that in the general population. Thus, the specificity of the FEBG-OAG was at least 78% or higher with stereophotography and with the imaging devices.

The FEBG-OAG based on stereophotographic evaluation or imaging devices did not classify any subject into a category for which treatment is advised (see Tabs. I and III). The stereophotograph-based guideline, however, classified more subjects with an abnormal ONH, while the imaging-device based guideline (MRA and OCT) classified more subjects with abnormal findings in nerve fiber layer (NFL) evaluation.

A strength of using these guidelines is that diagnostic errors based on only one criterion (or gold standard), which may jeopardize the quality of life of a subject, are minimized because 2 of 3 criteria must be met to initiate treatment. Otherwise, subjects may have suspected glaucoma, but no treatment is advised. In fact, the application of this liberal definition of specificity (based on procedure recommendations, see Tab. I) increases the specificity values to 100%. These results are in general agreement with the specificity reported by previous authors for photographic and imaging criteria (12).

In contrast, the diagnostic performance of the FEBG-OAG in the subjects from source 2 produced a high number of positives. Group 2 does not comprise a conventional "case glaucoma" group. This is a group with an expected high prevalence of glaucoma and includes glaucoma cases as well as normal subjects. Therefore, normal findings in source 2 are expected and they are not due to a lack of sensitivity because the source is not a glaucoma group, although the proportion of glaucoma subjects can be compared to that in the clinical setting of a glaucoma unit.

The distribution of patients according to application of the FEBG-OAG based on either method was fairly consistent: the concordance of diagnostic groups was 70.2% (patients on the diagonal of Tab. IV), whereas the concordance within a group with similar treatment advice was 70.5%. In every classification group, however, there were several findings that warrant special comment.

Central corneal thickness (CCT) in normal subjects (source 1, reference group) was 552.7±33.3 µm, which is a mean value that can be reasonably expected in subjects recruited from the general population. Comparatively, the patients referred for glaucoma evaluation (source 2) had thicker mean CCT values (564±39.6 µm), but the values did not differ significantly from those of the reference group.

The results of photographic and imaging evaluation of the subjects referred for glaucoma evaluation (source 2) indicated normal VF, ONH, and NFL in some subjects. Among the subjects in this category, some suspects with, for example, ocular hypertension, would be expected, as well as normal subjects that had been referred for evaluation. Some of these subjects may have been inadequately classified as ocular hypertensive due to thick CCT values. In fact, the suspects who fell in this category after imaging evaluation did have thicker corneas (577.7±38.0 µm) than those in the reference group from the general population ($p<0.05$). On the other hand, the photographic evaluation also showed thick mean CCT values (572.1±36.4 µm) in subjects with normal findings, but the difference from the control group was not significant.

On the contrary, patients fulfilling the 3 criteria of damage (VF, ONH, and NFL) had CCT values in the photographic and imaging classification of 542.6±37.7 µm and 536.5±34.1 µm, respectively. These values are almost the same as those of the reference group used for comparison with the general population. This was also observed in the groups with 2 of 3 criteria, for which treatment is advised based on the FEBG-OAG. These findings together support the notion that CCT is a confounding factor in glaucoma diagnosis.

It is interesting that some categories for which treatment

is not advised (unless IOP >30 mm Hg) might be "polluted" by the CCT confounding factor. These categories require only 1 of 3 criteria and these groups are therefore more susceptible to misclassification of some subjects. In both classifications, the finding of abnormal NFL (with normal VF and ONH) was associated with thicker mean CCT values than the categories with only abnormal ONH or VF, but the differences from the reference population were only significant in case of the photographic evaluation. Photographic evaluation of the NFL is more influenced by the observer than is OCT analysis and misclassifies more patients in this category with pre-perimetric glaucoma. This finding is supported by confirmation of the functional damage indicated by SWAP, which was 7% in cases classified by photographic evaluation versus 22% in the cases classified by imaging devices. Also, the mean NFL value measured by the GDx-VCC parameter, which is an independent device used for comparison among groups, was 18.7 in the photographic evaluation and 24.3 in the imaging devices.

The influence of subjective evaluation was also observed in the ONH evaluation. Imaging devices classified more subjects with abnormal ONH than photographic evaluation (see Tab. IV). Two of 4 subjects classified by photography were coincident with the imaging devices, while most of the patients classified by the imaging devices as having an abnormal ONH were classified by photography as having an abnormal ONH + NFL. The differences in this category (with the 2 criteria ONH and NFL) showed a similar trend as the abnormal ONH groups. The imaging devices classified 25 subjects in this group, while photography classified 51 patients, with 21 patients being classified the same by imaging devices and photography (Tab. IV). This is a group for which treatment is advised and most probably the imaging devices defined a group with more evidence of damage, as demonstrated by independent indicators, such as SWAP and GDx. The comparison between the photographic versus the imaging devices indicated that SWAP was altered in 41% versus 52%, respectively, and NFL was altered in 24.3 versus 30.8, respectively (see Tabs. V and VI).

The confounding factor in these groups is most likely the optic disc size due to the overestimation of ONH damage. The differences from the reference population were significant in the category of subjects with abnormal ONH (imaging devices) and the category of abnormal NFL and ONH (photographic evaluation): optic disc size was 2.5 and 2.4 mm^2, respectively, compared to 2.0 mm^2 in the reference population. Although optic disc size is a confounding factor in both cases, there are independent indicators of the presence of damage in the photographic evaluation, like NFL, that are significantly different from the reference population (NFL 24.3 in subjects with abnormal NFL and ONH in photographic evaluation versus NFL 14.5 in reference subjects). These differences also occur with the imaging devices, but in this case, the classification of subjects with abnormal ONH and NFL is less influenced by optic disc size.

In contrast, the differences in disc size between the reference population (2.0 mm^2) and subjects with normal ONH and abnormal VF and NFL were not significant, although mean optic disc sizes were smaller than those in the reference population (1.9 and 1.6 mm^2 in the photographic and imaging evaluations, respectively). Therefore, large optic discs have a much larger role in misleading the diagnosis compared to small discs.

In conclusion, the findings of the present study indicate that CCT and large optic disc size are confounding factors in glaucoma diagnosis. The MRA and OCT allow for objective implementation of the FEBG-OAG compared to conventional stereophotographic evaluation of the neuroretinal structures. Nevertheless, any diagnostic decision should be based on all the available data of a given patient to offer optimum assistance for visual problems.

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REFERENCES

1. Van Buskirk EM, Cioffi GA. Glaucomatous optic neuropathy. Am J Ophthalmol 1992; 113: 447-52.
2. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma: III: quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch Ophthalmol 1982; 100: 135-46.
3. Gaasterland DE, Blackwell B, Dally LG, Caprioli J, Katz LJ, Ederer F, Advanced Glaucoma Intervention Study Investigators. The Advanced Glaucoma Intervention Study (AGIS): 10: variability among academic glaucoma subspecialists in assessing optic disc notching. Trans Am Ophthalmol Soc 2001; 99: 177-84; discussion 184-5.
4. European Glaucoma Society. Terminology and Guidelines for Glaucoma, 3rd ed. Savona, Italy: Ed DOGMA; 2009: 117-57.
5. American Academy of Ophthalmology Glaucoma Panel. Preferred Practice Pattern: Primary Open-angle glaucoma Suspect. San Francisco, CA: American Academy of Ophthalmology; 2010: 18.
6. Tuulonen A, Airaksinen PJ, Erola E, et al. The Finnish evidence-based guideline for open-angle glaucoma. Acta Ophthalmol Scand 2003; 81: 3-18.
7. Shah NN, Bowd C, Medeiros FA, et al. Combining structural and functional testing for glaucoma detection. Ophthalmology 2006; 113: 1593-602.
8. Pablo LE, Larrosa JM, Polo V, Ferreras A, Alías EG, Honrubia FM. Performance of GDx and HRT in the Finnish evidence-based guideline for open-angle glaucoma. Eye 2010; 24: 297-303.
9. Heijl A, Lindgren A, Lindgren G. Test-retest variability in glaucomatous visual fields. Am J Ophthalmol 1989; 108: 130-5.
10. Caprioli J. Automated perimetry in glaucoma. Am J Ophthalmol 1991; 111: 235-9.
11. Wollstein G, Garway-Heath DF, Hitchings RA. Identification of early glaucoma cases with the scanning laser ophthalmoscope. Ophthalmology 1998; 105: 1557-63.
12. Budenz DL, Michael A, Chang RT, McSoley J, Katz J. Sensitivity and specificity of the StratusOCT for perimetric glaucoma. Ophthalmology 2005; 112: 3-9.
13. Polo V, Larrosa JM, Pinilla I, Pablo L, Honrubia FM. Optimum criteria for short-wavelength automated perimetry. Ophthalmology 2001; 108: 285-9.
14. Lin SC, Singh K, Jampel HD, et al, American Academy of Ophthalmology, Ophthalmic Technology Assessment Committee Glaucoma Panel. Optic nerve head and retinal nerve fiber layer analysis: a report by the American Academy of Ophthalmology. Ophthalmology 2007; 114: 1937-49.