Glaucoma detection with damato multifixation campimetry online

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CLINICAL STUDY

Abstract

Purpose To evaluate Damato Multifixation Campimetry Online (DMCO), a free-of-charge internet-based visual field test. DMCO exists in three versions: DMCO BASIC, DMCO STANDARD, and DMCO ADVANCED. The main focus was (i) to investigate the sensitivity and the specificity of the existing DMCO versions in the detection of glaucomatous visual field loss and (ii) to define and evaluate algorithms for the interpretation of DMCO results.

Methods The study design was an evaluation of a diagnostic test and included 97 individuals performing DMCO and white-on-white perimetry. Interpretation algorithms were devised to define abnormality, and these were evaluated using the Glaucoma Staging System as gold standard. Receiver operating characteristic (ROC) curves and area under the ROC (AUC) were calculated.

Results AUCs from 15 algorithms ranged from 0.79 to 0.90. The most promising algorithm combined results from two successive DMCO STANDARD tests. The sensitivity was highly dependent on the severity of glaucoma. Hence, for eyes with mild, moderate, advanced, and severe glaucoma, the DMCO test demonstrated a sensitivity of 11.8, 71.4, 100, and 100%, respectively. The specificity was as high as 98.1%. Median duration per eye to complete the DMCO STANDARD test was 86 s for the control group and 125 s in participants with glaucoma.

Conclusions DMCO shows promise as a free-of-charge online tool to identify glaucomatous visual field defects in a preselected population. Ongoing studies are evaluating the use of DMCO in a nonselected population.

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Introduction

The most common cause of visual field loss is glaucoma and approximately 50% of glaucoma

patients are unaware of any symptoms at the time of diagnosis.^{1–4} According to the World Health Organization, glaucoma is the commonest cause of irreversible blindness.⁵ It is estimated that by 2020, glaucoma will affect 80 million people and cause 11 million people to be bilaterally blind.⁶ The role of screening for glaucoma has been debated for several decades.⁷ Screening should ideally fulfill the following six criteria: validity, reliability, yield, cost, acceptance, and follow-up services.⁸ So far, no glaucoma screening program has met all the required criteria, and especially knowledge of the cost–benefit of a glaucoma screening program is lacking.⁹

Oculokinetic perimetry (OKP) has previously been suggested as a screening device for open-angle glaucoma in a systematic review.^{10,11} The manual version of this test is performed with a chart displaying multiple, numbered fixation targets located at strategic points in relation to a central, black test stimulus, which moves through known points in the visual field as the numbers are read by the patient.^{12–14} An automated version of OKP, the Damato Multifixation Campimeter Online (DMCO), has subsequently been developed.^{15,16}

The DMCO test results were presented as a map of the visual field with an indication of the points seen and the points missed. The blind spot was defined as one or more points located approximately 15° temporally. In the present form, DMCO does not indicate whether the overall result is normal or abnormal (Figure 1a).

The aims of this study were to develop and evaluate a protocol for screening for glaucoma using the DMCO. In Denmark, opticians and optometrists do not perform visual field testing due to legislation and financial interest. With future development, we hope that DMCO could become an easy applicable and non-expensive tool for the Danish optometrist society to use.

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Part of this work has been previously presented at the following meetings: Danish Glaucoma Association's seminar, Copenhagen, Denmark, 2012. European Association for Vision and Eye Research Meeting, Nice, France, 2013. European Glaucoma Society's Meeting, Nice, France, 2014. The Association for Research in Vision and Ophthalmology, Denver, USA, 2015.

Figure 1 (a) Damato Multifixation Campimetry Online (DMCO) STANDARD test printout. Masked information on the participant can be seen in the name box: Male, aged 48, and with a newly diagnosed glaucoma in the left eye. (b) Demographics at baseline, including information on doctor's diagnosis.

Subjects and methods

Study design and participants

The study population was recruited from patients attending a private eye clinic in Copenhagen, Denmark. The selection and grouping of participants was randomly carried out by a glaucoma specialist and was based on a full eye exam including optic disc evaluation and Humphrey Visual Field Analyzer 30 : 2 SITA Fast (HFA: Carl Zeiss Meditec, Dublin, CA, USA) printouts. The selection of participants took place in November 2010 and August 2011. The inclusion criteria comprised: minimum age of 18 years, familiarity with HFA, and visual acuity ≥ 0.5 (ie, 6/12). Exclusion criteria were: tunnel vision (ie, visual field <20 degrees), dense cataract, myopia >6 diopters, pregnancy, and physical circumstances preventing the participants from sitting correctly.

The participants were invited to participate in the study by letter. Approximately half of the invited participants had confirmed visual field defects typical of glaucoma such as nasal step or Bjerrum scotoma.^{17,18} The remainder

had ocular hypertension or other risk factors for glaucoma with normal visual field; these participants were used as controls.

The study was an exploratory analysis. As an initial power calculation would require knowledge of the variability of the various algorithms used to quantify the DMCO test, it was not possible to perform such in the present study.

Ethics Committee ruled that approval was not required for this study. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. All the participants signed consent forms, and the study was conducted according to the tenets of the Declaration of Helsinki.

DMCO

All DMCO examinations were performed in the same room, with normal lighting, using a Lenovo Think Pad T400 laptop (Lenovo International Limited, Morrisville,

NC, USA), a Logitech mouse (Logitech, Newark, CA, USA) and a 22" Philips Brilliance 220 SW computer monitor (Royal Philips, Amsterdam, The Netherlands), which were placed on a height-adjustable table. Participants were asked to wear their usual spectacles.

The test was accessed at www.testvision.org (Note: not all browsers can open the site). The website included written instructions, a demo movie, and a rehearsal program. DMCO exists in three versions: STANDARD, BASIC, and ADVANCED.¹⁶ These tests examine 42 points in the central 24° visual field. With the DMCO STANDARD version, a 0.2 s black-on-white stimulus is presented, whereupon the subject is required to move a computer mouse arrow on to the area of the stimulus. A smiley symbol appears if the computer mouse has been moved to the stimulated area, which when 'clicked on' prompts the appearance of the next stimulus. In the DMCO BASIC version, the smiley is replaced by a circle, in which a number briefly appears and disappears, simultaneous with the stimulus; when the subject moves the arrow into the area of the stimulus, a 'flower' appears with four numbered petals. Subjects are instructed to click on the same number as the one that had briefly appeared in the circle to confirm that they actually looked at the fixation target. In the DMCO ADVANCED version, the test strategy is similar to the STANDARD version, except that light-gray stimuli are initially presented, to increase sensitivity, with any missed points being re-tested using darker stimuli. The DMCO test does not have reliability indicators.

The participants were asked to read the online instructions, which were written in English. If the participant could not understand English, the instructions were translated orally into Danish. After an initial rehearsal, participants performed DMCO on both eyes, if meeting inclusion criteria. The non-test eye was occluded before each test. The correct working distance was determined by each participant by focusing at a fixation target and moving backwards and forwards until a large flashing stimulus disappeared into the normal blind spot. Each eye was tested a maximum of six times; three times with either DMCO BASIC or DMCO STANDARD version and followed three times with the DMCO ADVANCED version. Several tests were performed to study whether a learning curve for DMCO was present. The duration of each DMCO test was measured with a stopwatch.

Phase 1. Preliminary evaluation of DMCO BASIC, STANDARD, and ADVANCED versions

The phase 1 study was performed to evaluate which DMCO version showed the most promising results for further investigation. The data collection was planned

prospectively for DMCO and compared with retrospective HFA 30-2 SITA Fast data, which were performed within 6 months of the DMCO test. The examiner of DMCO was blinded to the participants' diagnosis and HFA results while administering DMCO. We considered the HFA result reliable if the following conditions were met: pupil size ≥ 2.5 mm; false-positive rate $\leq 15\%$; and false-negative rate $\leq 30\%$. Fixation losses and the Glaucoma Hemifield Test were not considered. Personal information was masked on the HFA printouts before being analyzed according to the Glaucoma Staging System (GSS).¹⁹ GSS can be used as a standardized method to quantify the degree of glaucoma. In this matter, the GSS classifies the HFA results into six categories: stage 0 (ocular hypertension/earliest glaucoma); stage 1 (early glaucoma); stage 2 (moderate glaucoma); stage 3 (advanced glaucoma); stage 4 (severe glaucoma); and stage 5 (end-stage glaucoma/blind).

A computer performed the actual comparison by comparing the number of points missed on a DMCO test with the GSS categories achieved.

Phase 2. Preliminary studies to determine the best method of maintaining correct working distance

The phase 2 study aimed to determine the best method of maintaining the correct working distance. Participants were positioned by using a proprietary chin rest or by placing a standard 1.5 l (32 cm) soft-drink bottle underneath the chin, which was either left in place throughout the test or removed once the correct working distance had been determined. Data collection was planned prospectively, and, due to practicalities at the clinic, both the DMCO STANDARD tests and a new HFA 30 : 2 SITA Fast were administered by the same examiner in 1 day, without blinding. Personal information was masked on the HFA printouts before being analyzed according to the GSS.

Phase 3. Development of DMCO algorithms for defining abnormality

The phase 3 study aimed to identify the best algorithm for defining DMCO abnormality. Overall, the algorithms were based on number of missed points in each examination. With DMCO STANDARD and BASIC tests, points seen and points missed were scored as 0 and 1, respectively, to provide the sum total of points missed (Figure 1a). With the DMCO ADVANCED test, each light-gray stimulus that was missed was re-tested with a dark-gray stimulus and then a black stimulus. The result was given a value of 0 if the light-gray stimulus was seen, 1 if the dark-gray stimulus was seen, 2 if only the black stimulus was seen, and 3 if the black stimulus was also missed.

The results of repeated DMCO examinations were evaluated to determine whether combined tests could improve the sensitivity and specificity of DMCO. When combining results from multiple DMCO examinations, the first test distinguished normal from 'suspicious' visual field. The suspicious visual field defects were then re-evaluated a second or third time to further distinguish normal from abnormal results. The algorithms created this way either combined first and second test (for example: DMCO STANDARD 1+2), or combined first, second, and third test (for example: DMCO STANDARD 1+2+3). By calculating the sensitivity and specificity according to GSS (we used stage 0 versus all other stages), the exact cutoff in terms of missed points on a DMCO test could be obtained. This cutoff categorized the DMCO result as normal or abnormal. According to the STARD guidelines, our rationale for DMCO test positivity cutoffs was exploratory, whereas the GSS cutoff can be considered pre-specified.²⁰

Because GSS is not widely used in clinical practice; we included a comparison of GSS to doctor's diagnosis in the results section (Table 1a). This table identifies the degree of glaucoma according to GSS and the ophthalmologist.

Statistics

Statistical analysis was performed using the R software package, version 3.0.2 (The R Foundation for Statistical Computing, www.r-project.org). We included all performed DMCO tests in the analyses and did not account for any missing data. All reliable HFA tests were included in the analyses and the non-reliable HFA tests were not accounted for in the analysis. Receiver operating characteristic (ROC) curves were derived for model discrimination of DMCO, assessed by area under the curve (AUC). AUC values close to 1.00 represented optimal discrimination, whereas values close to 0.50 indicated total lack of discrimination. ROC curves were used to optimize sensitivity and specificity. The avoidance of false positives was considered to be of paramount importance; therefore, emphasis was placed on high specificity. Ninety-five percent confidence intervals were calculated for the sensitivity and specificity of chosen DMCO cutoff values. The tests durations of the different DMCO versions were compared using Mann-Whitney rank-sum tests of continuous variables. Two-tailed *P*-values <0.05 were considered statistically significant.

Table 1a Comparison of doctor's diagnosis to GSS

	GSS staging											
	0 = ocular hypertension/earliest glaucoma		1 (early)		2 (moderate)		3 (advanced)		4 (severe)		5 (end-stage)	
	N	%	N	%	N	%	N	%	N	%	N	%
Eyes in total	84	100	26	100	21	100	15	100	17	100	2	100
Normal	67	79.8	7	26.9	0	0	0	0	0	0	0	0
Borderline	9	10.7	8	30.8	1	10.6	0	0	0	0	0	0
Glaucoma	8	9.5	11	42.3	20	95.2	15	100	17	100	2	100

Abbreviation: GSS, Glaucoma Staging System.

Table 1b Sensitivity and specificity after performing DMCO algorithm (Algorithm = DMCO standard 1+2) in comparison with GSS

	GSS staging									
	0 = ocular hypertension/earliest glaucoma		1 (early)		2 (moderate)		3 (advanced)		4 (severe)	
	N	%	N	%	N	%	N	%	N	%
Eyes in total	53	100	17	100	14	100	11	100	11	100
DMCO normal	52	98.1	15	88.2	4	28.6	0	0	0	0
DMCO abnormal	1	1.9	2	11.8	10	71.4	11	100	11	100

Abbreviations: DMCO, Damato Multifixation Campimetry Online; GSS, Glaucoma Staging System.

Figure 2 Flow diagram illustrating the Damato Multifixation Campimetry Online (DMCO) study design. During phase 1, the participants tested either DMCO BASIC or STANDARD and then went on to the ADVANCED version. The participants performing DMCO BASIC in phase 1 were invited to participate in phase 2 in which different devices were tested with DMCO STANDARD.

Results

Phase 1. Preliminary evaluation of DMCO BASIC, STANDARD, and ADVANCED versions

The recruitment took place from November 2010 to September 2011. A total of 123 patients were invited to participate in this study and 100 accepted. Detailed information on the participants and the DMCO testing can be viewed in the demographic table and the flow diagram (Figure 1b and Figure 2).

Fatigue was noticed among the participants as the number of participants performing the three tests declined. No adverse events were observed during either the performance of DMCO or the Humphrey.

A total of 170 HFA printouts were considered reliable and therefore included in this study. Of these, a match with the DMCO testing was found in 165 eyes. The Mean Deviation of the HFA and the number of DMCO missed points increased according to GSS stages (data not shown).

The DMCO test durations were assessed according to diagnosis and DMCO version. In the control group, the median DMCO completion times were 152 s (range, 82–605) for DMCO BASIC, 86 s (range, 46–643) for DMCO STANDARD, and 113 s (range, 41–742) for DMCO ADVANCED. In the glaucoma group, the median DMCO completion times were 190 s (range, 108–605) for DMCO BASIC, 125 s (range, 58–457) for DMCO STANDARD,

and 218 s (range, 70–742) for DMCO ADVANCED. For all the DMCO test versions, completion time in the control group was significantly less than completion times in the glaucoma group (Mann–Whitney, $P < 0.0001$). In addition, the completion time for the control group with DMCO STANDARD was significantly less when compared with the control groups with DMCO BASIC and DMCO ADVANCED (Mann–Whitney, $P < 0.0001$; data not shown).

Phase 2. Preliminary studies to determine the best method of maintaining correct working distance

Thirty-one participants who had performed the DMCO BASIC test in Phase 1 and who had reliable HFA results were invited to participate in Phase 2; of these, one participant died, four participants declined further testing, and 26 accepted. Fifty-one eyes of these participants were re-tested with DMCO STANDARD (Figure 2).

In phase 1, the blind spot was missed with a frequency ranging between 18.3 and 28.3% for participants tested with DMCO STANDARD. Most of the missed blind spots occurred in the control group (33.3–39.6%), whereas the borderline group (12.5–31.3%) and the glaucoma group (2.0–22.4%) were better at detecting their blind spot. In phase 2, between 21.6 and 23.5% missed the blind spot, again most missed blind spots occurred in the control group (30.0–33.3%; data not shown).

Finally, phase 2 sought to determine whether a more reliable result could be obtained by adding a chin stabilizer. Three different types of chin stabilizers were examined. No difference was found in between the tested stabilizers, and no difference from the test results obtained without a chin stabilizer was found (results not shown). As the evaluation of stabilizers in phase 2 were performed in a similar way as in phase 1, and as the results showed a similar fatigue pattern, the DMCO STANDARD results were pooled (Table 2).

Phase 3. Development of DMCO algorithms for defining abnormality

The 15 algorithms achieved AUC values between 0.79 and 0.90 (Table 2). The AUC values for algorithms with DMCO STANDARD demonstrated the highest discriminatory ability, with results ranging from 0.88 to 0.90.

Detailed information on the performance of chosen algorithms for each version of DMCO is presented with the corresponding ROC curves in Figures 3a and b.

The proportion of eyes classified as normal or abnormal according to the chosen DMCO STANDARD algorithm (DMCO STANDARD 1+2) is demonstrated for each GSS

Table 2 AUCs for DMCO algorithms and doctor's diagnosis

DMCO version	Attempt	AUC
BASIC	1	0.79
BASIC	1+2	0.85
BASIC	1+2+3	0.84
STANDARD	1	0.89
STANDARD	1+2	0.90
STANDARD	1+2+3	0.88
STANDARD 'Free position'		0.81
STANDARD 'Chin-rest'		0.82
STANDARD 'Bottle'		0.86
STANDARD pooled ^a	1	0.88
STANDARD pooled ^a	1+2	0.89
STANDARD pooled ^a	1+2+3	0.89
ADVANCED	1	0.86
ADVANCED	1+2	0.85
ADVANCED	1+2+3	0.83
Doctor's diagnosis		0.89

Abbreviations: AUC, area under the curve; DMCO, Damato Multifixation Campimetry Online. ^aPooled results from all DMCO STANDARD tests.

stage in Table 1b. Doctor's diagnosis in comparison with GSS stage is included in Table 1a.

Discussion

This study aimed to evaluate and develop a protocol for screening for glaucoma with DMCO. To increase the probabilities of successful evaluation, 15 algorithms were designed to distinguish normal from abnormal results.

Judged by AUC curves, the most promising algorithm was DMCO STANDARD 1+2, which achieved the highest AUC (Table 2). The main focus of performance evaluation was prevention of a high number of false-positive tests. In this matter, DMCO STANDARD 1+2 maintained a specificity of 98%. The sensitivity was 11.8% for eyes with mild glaucomatous visual field loss, 71.4% in eyes with moderate loss, and 100% in eyes with advanced or severe visual field loss. Even though the number of false negatives was unsuitably high in mild glaucoma cases, it is evident from other studies that a significant number of glaucoma cases remain undetected, both in moderate and advanced cases.²¹ Therefore, a screening tool such as DMCO requires a high specificity at the expense of sensitivity. In other words, as long as the test is inexpensive, any significant action to trace treatable glaucoma should be considered as long as it does not overload the health-care system with false-positive cases.^{9,22}

The choice of gold standard influences the decision as to whether the test under investigation is reliable.²³ By analyzing our results according to GSS, we used a rather rigorous gold standard. GSS enabled us to stage

Figure 3 (a) Receiver operating characteristics (ROC) curves, plotting sensitivity and 1-specificity for the three algorithms combining attempt number one and two. Damato Multifixation Campimetry Online (DMCO) BASIC 1+2, DMCO STANDARD 1+2, and DMCO ADVANCED 1+2, respectively. Area under the curve (AUC) is hatched. (b) Detailed information accompanying Figure 2a on the performing algorithm for each DMCO version: the exact cutoff of the test, sensitivity, and specificity, respectively.

participants in a retrospective manner without subjective clinical judgment by a physician, thereby making a blinded study possible.¹⁹

The main strengths of this study are the large number of patients and the use of HFA as the reference standard. Our study has several weaknesses. The apparent success of DMCO may have been biased by the exclusion of patients who had not previously produced reliable HFA results. Conversely, previous experience with HFA, which requires the patient to keep the eye still throughout the test, may have made it difficult for patients to cooperate with DMCO, which requires the patients to move the eye during the examination. Another limitation is that the DMCO results were reported with patients whose data were used to develop the optimal algorithm for defining abnormality. Furthermore, a weakness of the study is that evaluation

was done in an eye clinic and not in community optometry practices, which is where the deployment of this test is intended.

Finally, a limitation of the study was the use of a preselected population with a high prevalence of disease, which probably biased a falsely high sensitivity of the DMCO test. The low number of control eyes in our study may have exaggerated the specificity of this test. Additional bias possibly has occurred because we evaluated eyes, not participants.

In Denmark, most people have access to a personal computer, and therefore computer illiteracy is very low. However, the portion of elderly with poor computer skills remains a consideration when introducing DMCO as a screening tool to detect visual field defects. Nevertheless, computer illiteracy naturally becomes less a problem considering the natural course of life. The same

considerations can be made for the use of DMCO in the developing world, where both illiteracy rates and computer illiteracy rates decrease on a daily basis.

As no comparative studies on DMCO have previously been performed, the presented results are novel and should be confirmed and supported in subsequent investigations. However, more projects have explored the precursor of DMCO, the manual hand-held chart, OKP. In these studies, the majority of participants were preselected, often from a hospital setting. The sensitivities reported varied from 25 to 95%, whereas the specificities ranged from 56 to 99%.^{24–30} Three studies investigated OKP as a screening device, and reported similar results with sensitivities from 35 to 92% and specificities from 90 to 96%.^{31–33}

The concept of using a quick visual field test as a screening tool for glaucomatous defects is not new. Several studies have investigated the role of frequency-doubling technology (FDT) as a screening tool for glaucoma. Like OKP, FDT has been mentioned in a systematic review as a potential screening device.^{10,11} The studies revealed wide variation of FDT performance and the reported sensitivity and specificity ranged between 19 and 99%, and 57 and 87%, respectively.^{33–37}

The novelty of DMCO compared with the previous evaluations of possible visual field tests is simply related to its free accessibility. However, continuous improvement of the website is important and necessary to implement DMCO as a diagnostic tool. Hence, in the case of DMCO, a user-friendly website should be developed and general information on the need for minimal computer skills should be highlighted. Furthermore, a film tutorial would heighten the ease with which participants learn how to perform DMCO. Finally, a stopwatch and information on the algorithm could be of interest.

Considering that DMCO potentially could be used in developing countries, as a screening tool, a study concerning the performance of DMCO on cataract patients could be highly relevant. This would clarify the potential number of false-positive cases due to cataract, and further investigate whether DMCO could be a useful tool in these populations.

It is important to emphasize that we are not recommending DMCO as a substitute for conventional perimetry. DMCO could be useful in situations where conventional perimetry is not accessible. We believe that screening for only moderate and advanced visual field loss is probably more fruitful than attempting to detect early defects.²²

We would like to highlight that this was an explorative study, therefore no generalization can be made. On the basis of the present promising validation of DMCO in a preselected population, there is scope for

further evaluation of DMCO both in a selected population and in a nonselected population in the community. In this matter, we are currently preparing such study in which the herein optimized algorithm will be used to test random customers in Danish optician shops.

In conclusion, our findings suggest that DMCO may be useful for detecting moderate and severe glaucomatous visual field loss in situations where other forms of perimetry are not accessible.

Summary

What was known before

- Damato Multifixation Campimetry Online (DMCO) is accessed at www.testvision.org. It is a free-of-charge tool to detect visual field defects.
- Relatively little is known about the use and interpretation of DMCO.
- No previous validation has been performed.

What this study adds

- Interpretation of algorithms for DMCO with specific information on cutoff, sensitivity, and specificity.
- DMCO may be a future cost-beneficial method to detect unrecognized visual field defects.

Conflict of interest

The authors declare no conflict of interest.

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