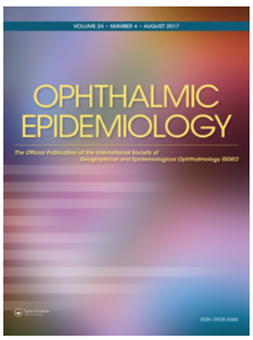

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ORIGINAL ARTICLE

Utility of 1% Tropicamide in Improving the Quality of Images for Tele-Screening of Diabetic Retinopathy in Patients with Dark Irides

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ABSTRACT

Purpose: To compare the quality of fundus photographs taken before and after instillation of one drop of tropicamide.

Methods: The 45° fundus photographs were taken with a non-mydriatic fundus camera in three conditions of the pupil; pre-mydriatic, 10 minutes after one drop of tropicamide, and fully dilated. Two photographs were taken in each condition; one centered on the macula and the other on the optic disc. Two vitreoretinal specialists graded the images.

Results: A total of 1768 fundus photographs of 149 diabetic patients with dark irides were included. There were more ungradable images (38.1% and 50.3%, graders 1 and 2, respectively) in the non-mydriatic state than partially- (4.6% and 11.5%) or fully-dilated (15.4% and 10.0%) conditions ($p < 0.001$, both graders). Partially and fully dilated states had similar rates of ungradable images ($p = 0.56$ and $p = 0.54$, graders 1 and 2, respectively). Test–retest reliability (repeatability) was 92.5% and 74.3% for the two graders, respectively. Inter-grader agreement was moderate (Kappa = 0.50).

Conclusion: Non-mydriatic fundus photographs have a high rate of ungradable images in patients with dark irides. Instillation of only one drop of tropicamide improves the quality of fundus photographs, which is not furthered by adding more drops. This strategy can be used in tele-ophthalmology programs.

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Introduction

Diabetic retinopathy (DR) is one of the leading causes of low vision and blindness worldwide.[1] About 171 million people worldwide were affected with diabetes in the year 2000, and this number is projected to increase to 366 million by the year 2030. It is estimated that developing countries will have a greater increase in and a younger population of diabetic patients by that time.[2]

Annual eye examinations and funduscopy with pupil dilation is recommended in diabetic patients for early detection of DR. However, ophthalmic services are limited and are not available to all patients. It is estimated that as many as 40–50% of diabetic patients are not screened annually because of a lack of resources or non-adherence to recommended guidelines.[3] Tele-ophthalmology is a cost-effective means of screening for DR and may reduce the burden of travel and save time for both patients and care providers.[4] Tele-ophthalmology has the potential to improve adherence to the recommended guidelines.

In a tele-screening program, a technician takes fundus photographs in the absence of an ophthalmologist and submits them to a reading center; in this situation, pupil dilation for taking photographs without examination of the anterior segment of the eye poses the risk of causing acute angle closure glaucoma in predisposed eyes.[5] Non-mydriatic fundus cameras are used in tele-screening projects both to save time and to remove the need for pupil dilation. Fundus photographs taken in a non-dilated state have been reported to be unreadable in 25% of cases.[6,7] These reports are from countries where most people are fair skinned with light irides. The problem may be of greater magnitude in populations with dark irides. We did not find any reports considering the effect of mydriasis on image quality from countries where patients are mostly dark skinned with dark irides.

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It has previously been demonstrated that instillation of only one drop of a mydriatic agent does not cause angle closure in susceptible eyes.[8] So this step is safe enough to be used in tele-screening projects and may improve the yield of readable fundus photographs.

The present study was designed to evaluate the percentage of poor quality images in fundus photographs taken without mydriasis from diabetic patients with dark irides and to see if this rate can be improved significantly when photographs are taken 10 minutes after instillation of only one drop of 1% tropicamide. Another purpose of the study was to explore whether the results can be further improved with complete dilation of the pupils, i.e. images taken 30 minutes after instillation of 3 drops of 1% tropicamide.

Materials and methods

Participants in this study were adult patients with a definite diagnosis of diabetes mellitus who were referred for ophthalmic examination to Hasheminejad Hospital in Mashhad, Iran, from two diabetes clinics, between January 2013 and March 2014. Medical histories of patients and results of ophthalmic examinations were documented and were later transferred to software specifically developed for the project on tele-screening of DR in Mashhad.

Non-stereoscopic, 45° fundus photographs were obtained by a trained photographer with a non-mydriatic fundus camera (Canon CR2-45NM fundus camera; Canon Inc., Tokyo, Japan) under ordinary room lighting. Three sets of images were taken of the same eye; baseline without dilation, partially dilated (10 minutes after one drop of mydriatic tropicamide 1%), and fully dilated (30 minutes after instillation of 3 drops of tropicamide 1%). Pupil size was not measured either before or after instillation of drops. At every step, two photographs were taken of each eye, one centered on the macula and one on the optic disc. The photographer was instructed to obtain good quality images and was allowed to take as many photographs as considered necessary to choose an acceptable image for tele-screening. Images were taken in a specific order; right eye before left eye, and macula-centered images before disc-centered images. Cases with media opacities were not excluded from analysis because our aim was to explore the effect of instillation of one drop of tropicamide on the quality of photographs in a real world setting. All photographs were stored in pre-designed software without any change to the original resolution and quality.

Slit-lamp examination and tonometry were performed before pupil dilation, and dilated funduscopy by a retinal specialist in the same session. Anterior segments of the eyes were examined for the presence of shallow anterior chambers before instillation of mydriatic drops. Cases predisposed to angle closure were excluded from the study.

All photographs were reviewed independently by two retinal specialists in an normally-lit room on a liquid crystal display (LCD) monitor (17-inch LCD Monitor, LG Inc., flatron, Beijing, China) using predesigned software. Graders were allowed to enlarge the images and adjust the brightness of the monitor. Photographs were presented randomly by the software and the readers were masked to the condition of the pupil at photography. Graders were permitted to restart the grading process if they considered it to be necessary. Each reviewer graded the image sets at least twice; the first grading was considered part of the training process and was not used in the study. The reviewers were allowed to discuss equivocal images with each other and improve their grading accuracy during this training process. The quality of each image was graded as good, poor or ungradable based on the following criteria: Good quality images were images without any artifacts or light reflex, with good focus and distinct and obvious details; poor quality images were defined as images with artifacts or flashlight reflex, or unfocused images which were not perfect, but had enough quality to confirm the presence or absence of DR; an ungradable photograph was defined as an image in which the presence or absence of DR could not be ascertained. If the quality of an image was sufficient to decide about the presence or absence of DR the image was not graded as ungradable even if determining stage of DR was not possible. To assess intra-grader repeatability, the software randomly presented 10% of images two or three times to each observer during the process of grading.

Separate analyses were carried out for each grader. Differences between conditions and locations were tested using the χ^2 test. The kappa coefficient was used to measure correlation between graders. Statistical significance was set at $p < 0.05$, and statistical analysis was performed using SPSS, version 11.5 for windows (SPSS Inc, Chicago, IL, USA). The study was approved by the Institutional Review Board of Mashhad University of Medical Sciences and adhered to the tenets of the Declaration of Helsinki.

Results

A total of 1,768 photos from 149 patients were graded. Twenty photos were lost because of operator mistakes or lack of patient cooperation. The maximum number

of images taken for each position was 3–4, among which the best image was chosen for the study. Patients (79 females, 70 males) had an average age of 43 ± 14.5 years. Overall, 13% of eyes (39 eyes) were pseudophakic, and 39% of patients (58 cases) had cataract (of any degree and any type). A total of 39 patients (26.2%) were affected by DR in at least one eye in clinical examination and 1.3% of patients (2 cases) had vitreous hemorrhage.

Grader 1 graded 20.6%, 67.8% and 11.6% and grader 2 graded 34.5%, 41.2% and 24.3% of all photos as good, poor and ungradable, respectively. The corresponding numbers for each pupil state are shown in Table 1. The difference in quality assessment was statistically significant between the non-dilated state and both partially- and fully-dilated conditions ($p < 0.001$ for both graders), but it was not statistically significant between partially- and fully-dilated states ($p = 0.56$ for grader 1 and $p = 0.54$ for grader 2, χ^2 test).

The difference in image quality according to image position (macula- and disc-centered) was also statistically significant for each grader without considering the dilation state of the pupil ($p < 0.001$), macula-centered images being more readable than disc-centered images (Table 2).

The inter-rater agreement (Kappa) for image quality was moderate (Kappa = 0.50). A total of 134 and 148 photos were presented repeatedly to graders 1 and 2, respectively, for evaluation of the intra-grader test of retest reliability (repeatability). Test-retest reliability was 92.5% for grader 1 and 74.3% for grader 2.

Discussion

In this study there were more ungradable images (38.1% and 50.3% for graders 1 and 2, respectively) in the undilated than partially- (4.6% and 11.5%) or fully-dilated (15.4% and 10.0%) states of the pupil ($p < 0.001$ for both reviewers). The difference between fully- and partially-dilated states with regard to the proportion of ungradable images was not statistically significant. Good quality images were also reported significantly more in the partially- and fully-dilated states of the pupil than in the undilated state by both reviewers. In the undilated state only 11.5% and 13.8% of photos were graded as good quality by the two graders, increasing to 37.8% and 43.8% in photos taken after instillation of only one drop of tropicamide.

One of the strengths of the current study is that our criteria for labeling a photograph as ungradable were relatively strict. Another strength is that our graders were vitreoretinal specialists. We requested the graders to imagine that they were in the position of a grader in the reading center and to label all photographs that had inadequate quality for ascertainment of the presence or absence of DR as ungradable, even if the image had good quality in terms of photographic aspects. On the other hand, photographs without good quality, but with visible retinopathy, were labeled as poor quality and not ungradable. Thus, poor quality images can still be used in tele-screening programs, but are not as informative as good quality images.

In studies evaluating the quality of fundus photographs, reported proportions of unusable images range from 4% to 25%.[4] These percentages are lower if photographs are taken with a dilated pupil. In the current study, 50.3% and 38.1% of non-mydriatic photos and 11.5 % and 4.6% of mid-dilated photos ($p < 0.0001$) were reported to be ungradable by the two graders, respectively.

The higher percentage of ungradable photos in the baseline condition in the current study may be related to smaller pupil size and possibly less cooperation by the patients relative to other studies. Another explanation is that photography was performed under normal room lighting, which is not the optimal condition for non-mydriatic fundus photography.

Pupil size changes with age, with smaller pupils being common in the elderly population.[9] Many theories have been proposed to explain the changes in pupil size with age and also in systemic diseases such as diabetes mellitus. These explanations include

Table 1. Quality assessment of fundus photographs according to pupil dilation in diabetic patients, Iran.

Photograph quality	Grader	Undilated, *n* (%)	Partially-dilated, *n* (%)	Fully dilated, *n* (%)
Good	1	68 (11.5)	221 (37.8)	171 (29.0)
	2	82 (13.8)	256 (43.8)	275 (46.6)
Poor	1	299 (50.4)	337 (57.6)	328 (55.6)
	2	213 (35.9)	262 (44.8)	256 (43.4)
Ungradable	1	226 (38.1)[a]	27 (4.6)[b]	91 (15.4)[c]
	2	298 (50.3)[a]	67 (11.5)[b]	59 (10.0)[c]

p-values between [a] and [b] or [c] were significant ($p < 0.001$), but *p*-values between [b] and [c] were not statistically significant ($p = 0.56$ for grader 1 and $p = 0.54$ for grader 2, χ^2 test).

Table 2. Quality assessment of fundus photographs according to image position without consideration of dilation level in a diabetic population, Iran.

Photograph location	Grader	Photograph quality, *n* (%) Good	Poor	Ungradable
Macula-centered	1	311 (34.8)	449 (50.3)	133 (14.9)
	2	353 (39.5)	389 (43.6)	151 (16.9)
Disc-centered	1	202 (23.1)	533 (60.9)	140 (16.0)
	2	260 (29.7)	342 (39.1)	273 (31.2)

Difference in image quality according to image position (macula- and disc-centered) was statistically significant for each grader ($p < 0.001$, χ^2 test).

atrophy of the sphincter muscle, and changes in sympathetic and parasympathetic tone.[10] Diabetic patients have smaller more rigid pupils. There is a general belief that women and myopic eyes have larger pupils, and men and eyes with darker irides have smaller pupils in room light.[11] In a study by Winn and colleagues, pupil size showed no correlation with sex, refractive error, or iris color.[9] Bergamin and colleagues studied the effect of iris color on pupillary light reflex and found that iris color significantly influenced the amplitude and velocity of pupillary contraction; faster and prolonged pupillary contraction was a significant finding in the brown iris group compared to the blue iris group.[12] Klein and co-workers found that patients with brown irides experienced more discomfort from the light of a flash than patients with blue irides.[13]

In this study, test–retest reliability (repeatability) was 92.5% and 74.3% for graders 1 and 2, respectively. The inter-grader agreement was moderate (Kappa = 0.50). As the criteria for grading images as good, poor, and ungradable were qualitative and newly described, this may have limited inter-grader agreement.

Lamirel and co-authors explored factors affecting quality of fundus images taken in an emergency room by nurses.[14] The study used a 5-point quantitative scale for grading quality of images, and intra- and inter-observer agreements between graders were very good (0.84–0.87). Image quality of the optic disc area was better than other areas of the retina, and younger individuals and people of black race had better quality photos.[14] Gupta and co-authors reported that the high rate of poor quality photographs and low sensitivity of diagnosis by non-mydriatic digital imaging limited the use of this technique as a perfect screening tool, particularly in diabetic populations with dark irides. The rate of ungradable images was around 31% in that study.[15]

In the current study, macula-centered photographs had a lower percentage of ungradable images than disc-centered photographs. This may have been due to the fact that taking a macula-centered image is easier and needs less cooperation by the patient than a disc-centered image. Another reason may be that in this study the disc-centered images were taken after the macula-centered images and the bright flash of the camera used for taking the first macula-centered image may have caused some inadvertent miosis or patient non-cooperation which could have degraded the quality of the disc-centered images. Another explanation is that the absence of macula and retinal area temporal to the disc in some disc-centered images may have precluded ascertainment of the presence or absence of DR.

One of the major limitations of the current study is that all patients were imaged under normal light conditions. Performing non-mydriatic fundus photography under dark room conditions may maximize pupil size and improve image quality. This could explain a part of the much higher rate of ungradable images in the non-mydriatic state than those found in prior studies. Another limitation of the current study is that there was no assessment of pupil size under each of the conditions, which would have added valuable information. However, as the purpose of the current study was to explore the utility of the strategy of "mini-dilation" in a real world tele-screening program and not to determine the best size of the pupil to obtain adequate image quality, this measurement was not performed. We also did not document dark irides clinically, but this study presumes that most participants had dark irides due to the composition of our patient population in Iran.

As a result of the increasing prevalence of diabetes mellitus and the need for regular ophthalmic examinations in affected individuals, there is an increasing burden on the ophthalmic community for undertaking these screening examinations. Tele-screening, which is a well-suited solution for this problem, must have high sensitivity and sufficient specificity to not only find all eligible patients, but also reduce the burden of examinations. The presence of a high rate of ungradable images in a program means low specificity and if high sensitivity is planned, all patients with ungradable images must be referred for ophthalmic examination. Given the rates of ungradable images in the baseline (undilated pupil) examination of this study, at least 1/3 cases must be referred for examination for this reason. This group of patients must be added to those that are affected by retinopathy and will in total account for nearly half of all patients. This high percentage of referral is not reasonable in a screening program.

Pupillary mydriasis in eyes with shallow anterior chambers may cause pupillary block and incite an acute attack of angle closure glaucoma. In programs for tele-screening for DR, photographs are usually taken by trained personnel in district areas in the absence of ophthalmologists or optometrists and in the absence of ophthalmic equipment such as a slit lamp. So patients predisposed to angle closure cannot be easily diagnosed. Non-mydriatic fundus cameras are well suited to do the task without imposing the risk of angle closure attacks in a tele-screening project. However, as shown by the results of this study, this imaging technique may be accompanied by a high rate of unreadable photographs and consequently an unacceptably high rate of referral. It has been stated that

instillation of only tropicamide does not increase the risk of angle closure in susceptible eyes.[7] To increase the safety of patients and to reduce the time expenditure which is an important factor in a busy screening program, we examined if instillation of only one drop of tropicamide is enough to improve the quality of images to an acceptable level.

Based on the results of the current study, we recommend instillation of one drop of 1% tropicamide 10 minutes before taking photographs in tele-screening projects where there is a high probability of poor quality images in the non-mydriatic state.

Declaration of interest

The authors report no conflicts of interests. The authors alone are responsible for the writing and content of this article.

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