Detecting Progression of Nuclear Sclerosis

Human Grading Versus Semi-Automated Computer Grading

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ABSTRACT

Purpose: To compare semi-automated estimates (gradings) of nuclear sclerosis from digitized images with gradings of film-based images graded by human observers.

Methods: Film-based slit lamp images taken at baseline and at five and ten-year follow-up examinations of the Beaver Dam Eye Study cohort were digitized, and optical traces were taken along an axis through the center of the cornea and lens. Four indices of the severity of sclerosis were calculated based on the optical densities. The associations of the original Beaver Dam grades and these indices to age, vision, and subsequent change in severity of sclerosis over two subsequent visits were compared.

Results: At baseline photographs, the Spearman correlation between age and severity was 0.65 for the original film-based grading (n = 9518 right eyes) and varied between 0.46 to 0.71 for the measures from digitized images. Correlations of the indices to visual acuity were 0.38 for the film-based grading and ranged from 0.32 to 0.38 for the other indices.

Our assumption is that nuclear sclerosis does not regress and percent regression is a reflection of error in grading. Percent regression and progression of sclerosis over a five and a ten year interval was determined for each index. After five years, 48.2% progressed and 4.9% regressed using the Beaver Dam grades; progression occurred in 4.9% to 9.9%, and regression occurred in 4.5% to 7.0% for the other indices. After ten years, 61.9% progressed and 3.2% regressed using the Beaver Dam grades; progression occurred in 8.0% to 19.7%, and regression occurred in 2.6% to 9.7% for the other indices.

Conclusion: Semi-automated grading of the digitized images can be used to process thousands of images with little oversight by a trained grader. Indices of sclerosis that closely parallel human grading in their relationships to age and to visual acuity can be easily computed. However, the indices appear to identify significantly less progression of nuclear sclerosis compared to human grading.
INTRODUCTION

Nuclear sclerosis is progressive throughout life. While changes in the nucleus of the lens can be seen through a dilated pupil by trained observers, such changes are not usually labeled as cataract until there is obscuration of the discrete lamellae and sulcus of the lens nucleus. Progressive nuclear sclerosis may be associated with changes in refractive error and in visual acuity, as well as other measures of visual function. Nuclear cataract was the most common cataract to precede lens extraction in the Beaver Dam Eye Study cohort.¹

Several schemes have been developed to evaluate nuclear sclerosis for use in clinical and epidemiologic studies. Some are based on clinical examination.²,³,⁶ Because nuclear sclerosis is a slowly progressive process throughout life in Western populations, it is difficult to assign a change from examination to examination when the interval between examinations is relatively short, especially when there may be different examiners judging severity. Therefore, for most long-term longitudinal studies (e.g., for incidence studies or for clinical trials), photographic documentation has become the preferred technique for judging severity of nuclear sclerosis. Several protocols have been developed for photographic or other imaging documentation.⁷-¹⁰ Usually, the photographs are taken with a slit lamp camera which produces an image that replicates a clinical slit lamp view at the instant the photograph is taken. The advantage of these systems is that they produce images that are similar to the view of the lens as seen by a clinician at the slit lamp. Different systems have been developed to grade such slit lamp images.¹⁰-¹⁶ These systems are similar in that they entail comparing study photographs to sets of slit lamp photographic standards.

There are different choices of cameras available for slit lamp photography of the lens. Those cameras that are designed using the Scheimpflug principle, that is, the plane of the film parallels the optical section through the lens, can provide an evenly-focused representation of the section of the lens.⁷,⁹,¹⁴,¹⁷ Slit lamp cameras that use a conventionally-designed film arrangement,
that is, the film parallels the flat camera back and plane of the camera lens and the illuminated section of the lens is at 30 or 45° from the viewer or the camera, can provide an image with best focus corresponding to only part of the image of the lens (ideally the sulcus of the nucleus). Other parts of the image are not as well focused. The advantage of cameras of this design is that they are relatively inexpensive, readily available and, in general, they are reliable (or easily repairable) in a field setting.

Digital rather than film-based imaging systems have recently been used with Scheimpflug design cameras. Datiles et al. reported that by using such a system, variability in estimates of progression were decreased compared to a clinical grading system such that they were able to detect change in sclerosis over only a one-year interval. This system uses differences in density as measured in reflected light from an optical trace through the center of the lens as a measure of sclerosis. The outcome is a truly continuous measure, unlike the human grading systems, which measure against standard photographs. (Some investigators attempt to approximate a continuous measure with film-based human grading by having a grader estimate in tenths between standards.) The greatest disadvantage of the Scheimpflug digital system is its cost. Also, like other imaging/grading systems, it has difficulty in estimating the severity of sclerosis when other lens opacities are also present.

No matter which camera system is used, certain specific lens regions are more informative about the severity and change in severity of nuclear sclerosis (or lens density) than others. Qian et al. indicates that eliminating information from the lens cortex is important in defining a “common lens nuclear area” and measuring the optical density in that area. Duncan et al. defines a “region of interest” which similarly excludes the lens cortex. Within the nucleus there are identifiable regions of density both anterior and posterior to a central region of decreased density (sulcus). This defines the important parts of the lens for estimating the severity of nuclear sclerosis. Qian et al. has also suggested that densitometry, taking weighted
information from specific regions of the nucleus, may permit the detection of changes in nuclear density over a short period of time.²⁴

There are large epidemiologic studies and clinical trials that have been completed and others that are ongoing which employ the non-Scheimpflug slit lamp film-based camera technology with images graded by human graders.¹⁰,¹¹ The variability in the grading of such photographs leads to relatively broad confidence intervals in estimating prevalence of nuclear cataract, in estimating the strengths of association of a variety of factors to severity, and in measuring change over time. Gradings derived from semi-automated densitometry measurements of the photographs from these projects might diminish grading variability and, therefore, permit better estimates of change.

We have developed a semi-automated grading procedure for nuclear sclerosis from black and white digitized images that were derived from color based film images. We compare this technique with the results of human gradings of the original film based color images in data derived from a longitudinal population based study.

METHODS

Slit lamp photographs of the lenses of participants in the Beaver Dam Eye Study were taken at baseline and 5 and 10 years after. Signed consent was obtained from each participant at each examination. Institutional review board approval was obtained yearly. The tenets of the Declaration of Helsinki were adhered to. The age range of the 4926 persons seen at baseline was 43-86 years. The photographs were taken after pharmacologic dilation of the pupil with a specially modified Topcon slit lamp camera using Ektachrome 200ASA film. This camera is not designed according to the Scheimpflug principle. The camera was modified to fix the angle of the slit beam at 45° from the visual axis, the beam width fixed at .3 mm and height at 9 mm, and flash intensity was set at 5. The slit beam illumination was always to the left of the photographer. Unmovable fixation targets were added to the camera.¹⁰ The camera was
evaluated for these parameters every six months during the 2 1/2 years of each examination phase, or more frequently if any question about its function arose. The photographer was instructed to focus the camera at the sulcus of the lens nucleus. All photographs were developed by a commercial laboratory and sent to the study offices for grading the severity of sclerosis. The grading scheme required comparison of the participant’s photograph with photographic reference standards of increasing severity of sclerosis. Graders assigned a grade for the severity of sclerosis by comparing primarily the density of the sulcus and secondarily the distinctness of the other nuclear landmarks with those in standard photographs. The scheme resulted in 5 levels of increasing severity. The grader evaluated overall photograph quality and plane of focus of the image. The grader was masked to subject characteristics. Right and left eyes were graded independently. A quality control program for photography and grading was ongoing through all examination phases. Intergrader reliability was 64.7% for exact agreement and 99.8% within one category.10

The original images on film were first obtained during the 1988-90 examination. Digital imaging cameras were not widely available and were (and still are) costly. Our current aim was to take advantage of the many attractive features of digital techniques that are now available that might facilitate automated grading of our images. To do this, we had to digitize our film-based images. The scanner was chosen based on availability, cost, and reputed fidelity of the scanning process. We cannot directly compare our digitized film-based images with images taken originally with a digital slit lamp camera because we did not have one available. Because our comparisons are all done on images captured, processed and digitized the same way, our internal comparisons will be consistent.

The slit lamp photographic images were scanned into gray scale images with 256 integer levels using a Nikon Cool Scan LS-2000 (1.31 firmware, 2.5 software). The slides were removed from their stored plastic sleeves and placed face up, label to the right, scanning
parameters were selected for black and white scanning (see Appendix), the image was previewed to ensure that the slit lamp image was centered and that both the front and back edges of the image were contained within the desired “box”. The image was scanned and saved to a subdirectory and filed according to digit code. The quality control procedures entailed checking scanning parameters against the written protocols at the beginning of each session. The first scan of every session was a repeat of the last scan of the previous session. Rescanned photographs were visually inspected for any difference between it and the original scan. If no differences were found, the image was saved to a unique file. If any differences were noted on inspection, all parameters for the original and rescanned images were compared and the software and hardware were checked to determine if there were errors in the scanning parameters. Any corrections were made, and the image was rescanned until was judged to be the same as the originals. These adjustments were needed infrequently. The digital images were subjected to the following procedures: the location of the central axis (the horizontal axis connecting the center of the cornea and the center of the lens) was found and a trace of the optical density of the lens was obtained along that axis. *The trace values actually represent a “median” value (using the k medians approach) over an area around the axis.* Landmarks corresponding to the peak value for the cornea, anterior chamber, anterior surface of the lens, most anterior part of the lens nucleus, center of the anterior lentil, sulcus (between anterior and posterior lentil), center of the posterior lentil, posterior boundary of the nucleus, and the region just behind the posterior capsule were identified. These values were recorded automatically. Figure 1 is an example of the digitized image. The trace appears at the top of the figure. It is taken along the axis (1). Landmarks needed to assess severity of nuclear sclerosis are labeled (2, 3, 4). The processed images, by batch, were presented to the senior grader (AE) for approval or modification of the automated landmark placement. Such modification for landmarks relevant to calculating an index of sclerosis was needed in about 1.7% of images (Ferrier N, et al. *IOVS* 2002;43:ARVO
Abstract 435). Detection of photographic artifacts (including the “keyhole” shaped light artifact appearing in the anterior chamber) was built into the custom-designed program and were eliminated automatically. These techniques were applied to slit lamp images from participants in the Beaver Dam Eye Study at the baseline and at the 5- and 10-year follow-up evaluation. The total number of images examined was 20,093.

Gradings for each participant for each eye for the baseline examination were used in the initial comparisons of measures of sclerosis and in evaluating relationships to age and vision. For analyses of progression of sclerosis, gradings for 5-year and 10-year follow-ups were compared with gradings of the baseline photographs (measured using a modification of the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol).\textsuperscript{25}

**STATISTICAL ANALYSES**

The severity of nuclear sclerosis was taken to be represented by the relationship of the gray level between selected anatomic features of the lens. While several different combinations of these measurements are possible (and were tried), we present data for four models all of which were rescaled to 1 to 10:

1. \( \log \left( \frac{lentils - sulcus + offset}{sulcus} \right) \) Where the values for the lentils are the height of the peaks labeled 2 and 4 in Figure 1.

2. Area under the curve for the anterior lentil endpoints is taken from the trace segment corresponding to the anterior lentil in the digital image\textsuperscript{26} where the endpoints are defined by the gray level between the half height of the change from the lens cortex anterior to the anterior lentil (2 in Figure 1) in front and the half height of the line leaving that peak as it descends to the gray level of the sulcus (3 in Figure 1) separating the anterior from the posterior lentil.

3. \[ \left( \frac{\text{gray level at the height of anterior lentil curve segment} - \text{gray level at the height of sulcus + offset}}{\text{gray level at the height of posterior lentil curve segment} - \text{gray level at the height of sulcus + offset}} \right) \]
where the height is the “median” value of the maximum height.

4. Gray levels of anterior lentil, sulcus (3 in Figure 1) and posterior lentil (4 in Figure 1) (combined by the k medians approach)

For models 1 and 4, the individual measures of the lentils were combined to a single measure using k medians. The k medians calculation interpolates how far observed values are from “central” values on a predetermined scale, then weights the average of these values to arrive at a single value. The rationales for these four approaches to estimating severity are as follows:

1. Reflects the degree of optical definition of the lens landmarks. The more sclerotic the lens nucleus, the closer the lentils and sulcus are in value (more homogeneous)

2. Accounts for the amount of light that is reflected back from the anterior lentil

3. Describes a reflectance gradient from the relevant landmarks. As sclerosis progresses, there is a relative enhancement of the light reflected from the anterior compared to the posterior lentil

4. No adjustments are made to the raw values; they are combined for an overall estimate of reflectance.

The offset in approaches 1 and 3 refer to the median gray scale values measured in the anterior chamber. For these four measures, we used an arbitrary continuous scale of 1 to 10. Based on the minimum and maximum values in an initial test sample, the scaling factor was determined and applied to all final gradings.

The relationships between these measures of sclerosis and the original Beaver Dam gradings were assessed using Spearman correlation coefficients. Similarly, the relationships of each measure with age and visual acuity were evaluated using Spearman correlations.
The ability of a measure of sclerosis to detect progression was estimated by the difference in sclerosis between baseline and 5 years and between baseline and 10 years. Definite change in the continuous measures was based on a difference of two standard deviations of the change in a given measure between baseline and the 5-year follow-up for the population. This corresponds to a one-step change in the Beaver Dam grades (5 level scale) and a 2-step change for the other indices (10 level scale).

**RESULTS**

The measures of central tendency for the Beaver Dam grades (BDG) and other indices of sclerosis are given in Table 1. All indices except the BDG are continuous. Therefore, we give median values, means and standard deviations, and the coefficients of variation. For BDG and for index 3, there is a consistent increase over the three time points. The coefficients of variation decrease across the three time points for these two indices. *There are smaller numbers of lenses with Beaver Dam grades because film-based gradings were more often call “can’t grade” than semi-automated gradings. The Spearman correlation coefficients of the new indices to the Beaver Dam grades (BDG) are given in Table 1. Index 1 was most highly correlated with the BDG at each visit.*

Because nuclear sclerosis is an age-related phenomenon, we evaluated the relationships of the indices to age. The mean age in this population was 60.6 (11.3) years. The mean and modal values increase with age for all measures (Figures 2a, 2b). The Spearman correlation coefficient between age and the indices is given in Table 2. These vary between the indices. Correlation coefficients decreased from baseline to the 10-year follow-up visits, but the relative order within visits was the same. Index 1 was most correlated and index 3 was least correlated with age at all visits.

Nuclear sclerosis in its early stages has not been found to be a cause of visual impairment. The mean visual acuity in this population was 51.2 (15.1) letters of the logMAR
scale (Snellen equivalent of about 20/30) in right eyes. However, we evaluated whether there was a relationship of best corrected visual acuity as a continuous measure of functional ability and indices of sclerosis. Correlation coefficients of visual acuity and the indices are given in Table 2. The Spearman correlations between visual acuity and the indices of sclerosis ranged from 0.32 to 0.38. There was no consistent pattern of correlation between the three visits.

We next sought to evaluate the ability of the indices to detect change over 3 visits each 5 years apart. We report this as percent progressed and percent regressed as defined in Methods. These data, along with the coefficient of variation for change (Table 3), indicate that for index 1 and index 3 a slightly greater percent progressed than regressed and for index 2 and index 4 a slightly greater percent regressed than progressed after five years (Table 3). At ten years, most indices showed more progression than regression. The Beaver Dam grade showed substantially more progression than regression at the end of each interval even though the median change for the first five years was zero.

We examined the association of each of the derived indices with the Beaver Dam grade at the baseline visit using a regression model. Index 3 was most poorly associated with the Beaver Dam grades ($R^2 = 0.38$), while the other three indices were more closely associated with the Beaver Dam grades ($R^2 = 0.51, 0.43, 0.52$ for indices 1, 2, and 4 respectively). In addition, evaluating effect of focus and differing exposures indicated that index 3 was most variable in values of all the indices (data not shown).

It has been apparent to graders in our study that poorly focused photographs (not focused at the sulcus) yield more uncertainty about the severity of sclerosis. We found that the width of the corneal bright band, a reflection of the plane of focus of the photograph, was related to the estimated severity of sclerosis. A wide corneal width occurs with more posterior focus and was associated with increased estimates of severity. This was true for all indices (data not shown).
Attempts to systematically adjust the semi-automated gradings to account for this were not uniformly successful.

We have previously described a relationship of lens color to age. Lens color is graded from the same slit lamp photographs that is used to grade the severity of sclerosis.\textsuperscript{28} To evaluate whether lens color was influencing estimates of progression of sclerosis, we computed the percent of lenses whose severity of nuclear sclerosis regressed or progressed in those lenses where the color was the same at baseline and at follow-up visits. The percent regressed and progressed was nearly identical to the values given in Table 3 for all indices, including the Beaver Dam grade.

The Beaver Dam grades are discrete while the other indices are continuous. To evaluate how a more continuous human grade (decimalized system) compares to the indices, a subset of the Beaver Dam Eye Study slit lamp photographs was graded by a single grader from the Age-Related Eye Disease Study (AREDS) grading team using the AREDS grading protocol.\textsuperscript{11} The grader was masked to the Beaver Dam gradings. These gradings resulted in a pattern similar to that using the Beaver Dam gradings. Namely, these gradings were correlated with age and vision. Although we had such gradings at baseline and at the 5-year follow-up only, more progression than regression was found using this human grading system as well.

**DISCUSSION**

Grading schemes are most useful when variability is kept at a minimum so that prevalence, incidence and risk factor estimates can be identified and quantified. However, valid and reproducible techniques to document and to assign a severity level to nuclear sclerosis have been problematic. We attempted to diminish obvious sources of image variability in our study by fixing the mechanical settings of the slit lamp camera, adding unmovable fixation targets, changing flash bulbs periodically, maximizing pupil dilation, and standardizing the training program for photographers. Even so, there are differences in illumination, film emulsion and
processing, fixation, focus of the photograph, and pupil size from subject to subject and for the same subject at different times. Still, such photographic documentation of nuclear sclerosis appears to be useful for epidemiologic longitudinal studies.\(^8,11,13,21\) Scheimpflug photography may reduce some of the photographic artifacts because of the uniform plane of focus of the image of the lens nucleus and other lens landmarks. This may permit the detection of more subtle amounts of progression. However, well-trained graders have learned to discriminate some of the effects of photographic artifact on lens images and are able to reliably grade the less than perfect photographs of the lens from non-Scheimpflug images, resulting in the ability to detect age-related changes and progression.

In an attempt to maximize the amount of useful information while minimizing variability in our lens photographs, we embarked on the project we describe here. The resultant gray level data were analyzed using several different approaches to determine the optical densities of anatomic regions of the nucleus. Our algorithms then took ratios or differences in reflectance of various landmarks in the lens, adjusted for overall photographic illumination by taking into account the light reflected from the anterior chamber, and tested these resulting indices for their relationships to age, vision and change in estimated nuclear sclerosis over a 10 year time interval. While one or another index was more strongly associated with age, no index improved upon a human grading (BDG) when evaluating relationships to age, and no other measure identified as much progression. The automated grading was significantly more efficient in utilization of grader time than the standard method. The procedure referred to above enabled the senior grader to review all 20,000-odd images over approximately two months, interspersed with other projects. Balanced against this efficiency must be considered the effort to scan all of the slides in question.

We evaluated the relationships of the indices of sclerosis to vision, although we\(^29\) and others\(^30\) have not found these variables to be highly correlated. Of the indices we computed,
index 1 was most highly correlated with visual acuity and identified progression of sclerosis at each examination. While index 3 was more likely to identify progression at both follow-up examinations compared to index 1, it was not as highly correlated with age as index 1. Indices 2 and 4 showed no superiority over the other indices, and the coefficients of variation for progression for these indices were higher than for the other indices.

We made certain assumptions in identifying the measurements to be included in our indices of sclerosis. These included assuming that the clarity of the sulcus at the center of the nucleus and more homogeneous light scattering are typical of more severe nuclear sclerosis. However, lenses with apparently “smooth” nuclear areas can be seen at young ages when nuclear density is low. Also, “smooth” density with no obvious sulcus can occasionally be seen at older ages when there is more nuclear sclerosis. In such cases, using formulae which depend on finding a sulcus could produce inaccurate assessment.

We have made several assumptions in our study. First, we and others are limited by the lack of validating criteria. Thus, although progression of nuclear sclerosis with age is an observable clinical phenomenon, there is no way to document and quantitate this biochemically in vivo, and observable progression at the slit lamp requires years of observation. We made the assumption that sclerosis is progressive and that regression or improvement does not occur, so we regarded the latter change as error. Not only did we assume no observable change or progression over time was to be expected, but we also assumed that an index which detected a greater amount of change was a better measure of the underlying biology. It is possible that further attempts to identify and correct variability in how the lens is imaged might result in a more valid result. However, another approach to evaluating digitized images such as ours is the further development of a neural network like that described by Duncan et al. The underlying assumption for that approach is that the human grader is correct and that a semi-automated system can be “trained” to yield similar grades. Our assumption had been that an automated
uniform approach might improve upon human grading because it would reduce human grader variability. In fact, our findings indicate that the experience and judgment of human graders is desirable. Thus, it is possible that further development of the neural net approach to grading digital images or digitized images from film-based photographs will deliver a method that replicates human grading, but may do so more rapidly than humans. Fan et al. (Fan S. et al. An automatic system for classification of nuclear sclerosis from slit-lamp photographs. Medical Image Computing and Computer Assisted Intervention 2003, In Press) also has developed a model which assumes that human graders are correct in assigning grades of the severity of sclerosis. This has yielded promising results in a small validation sample (data not shown). Our conclusion is that, at this time, we plan to continue careful training of human graders for our film-based images of the lens nucleus. We will, however, continue to refine our algorithms for quantitating nuclear sclerosis from digitized images.
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FIGURE LEGEND

Figure 1. Example of scanned image used to grade nuclear sclerosis with axis and landmarks.

Figures 2a. and 2b. Mean (a) and Median (b) values for Beaver Dam grades (symbol = B) and each proposed index (symbol 1 through 4) by age.

Note: So that lines are not overlapping, a constant of 2, 4, and 6 was added to indices 2, 3, and 4 values, respectively, for display purposes only.
Table 1. Measures of central tendency for indices of nuclear sclerosis at baseline, 5 year, and ten year follow-up examination (right eyes).

<table>
<thead>
<tr>
<th>Visit</th>
<th>Index</th>
<th>N</th>
<th>Median</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Coefficient Variation</th>
<th>Correlation* with BDG†</th>
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<td>Baseline</td>
<td>BDG†</td>
<td>4518</td>
<td>2.00</td>
<td>2.44</td>
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<td>5 Year Follow-Up</td>
<td>BDG†</td>
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* Spearman Correlation Coefficient
† BDG = Beaver Dam Grade for nuclear sclerosis
Table 2. Spearman correlations of indices of sclerosis with age and visual acuity (right eyes).

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*BDG = Beaver Dam Grade for nuclear sclerosis
Table 3. Regression and progression of nuclear sclerosis for five and ten year intervals (right eyes).

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<th>N</th>
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Figure 1.
Figure 2a.
Figure 2b.