Image analysis of changes in drusen area

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Abstract. Computerized image processing was used to analyze color fundus photographs of 11 patients (22 eyes) with macular drusen who were followed for more than 2 years (mean follow-up, 4.7 years). Significant changes over time (more than ±20% of baseline area) were measured in the surface area of macular drusen in 18 of 22 (82%) eyes. An increase in the drusen area was associated significantly with eyes with mostly hard drusen and an initially smaller drusen area; but a decrease was associated with eyes with mostly soft drusen and an initially larger drusen area ($P<0.01$). The mean absolute rate of change in the drusen area was more than twice as great in eyes with mostly soft drusen compared with those with mostly hard drusen ($P<0.05$). All eye pairs studied showed a concomitant increase or decrease in the drusen area.

Key words: age-related maculopathy - drusen - fundus images - image processing.

Drusen are a clinical manifestation of age-related maculopathy (ARM). In the absence of other complications of this disease, drusen are associated with good visual acuity (Vinding 1990) and are highly prevalent in adult populations (upward of 85% by histology) (Hogan 1972; Coffey & Brownstein 1986; Lewis et al. 1986). Yet drusen are often complicated by retinal pigment epithelium (RPE) detachment (Gass 1972, 1973; Robinson & Gitter 1972; Kenyon et al. 1985), RPE atrophy (Sarks 1952; Willerson & Aaberg 1978), choroidal neovascularization (Sarks 1973; Teeters & Bird 1973; Sarks et al. 1980), and disciform degeneration (Gass 1973; Gragoudas et al. 1976; Sarks 1976). These conditions cause decreased vision, making ARM the most common cause of new blindness in the aged (Ghafour et al. 1983; MacDonald 1965). The prevalence of all types of ARM in developed countries is reported as 9-20% (Sorsby 1966; Kini et al. 1978).

The only advocated treatment of ARM is laser photocoagulation for specified cases with RPE detachment or choroidal neovascular membranes (Grey et al. 1979; Macular Photocoagulation Study Group 1986; The Moorfields Macular Study Group 1982; Robinson & Gitter 1972; Schatz & Patz 1973). Early intervention through either prevention or treatment of drusen (Gass 1973; Duvall & Tso 1985) will require detailed knowledge of pre-exudative phases of ARM.

Most clinical studies of drusen evaluation have used qualitative or, at best, semiquantitative methodology (Gass 1973; Gragoudas et al. 1976; Gregor et al. 1977; Ferris 1983; Strahlman et al. 1983; Smiddy & Fine 1984). Grading of drusen as larger or smaller than the standard, or finer grading using numeric scales, has been used to determine size, number, distribution, and confluence of drusen. These measures have been limited by human ability to assess area fractions. In this study, we used a computerized image-analysis technique (Peli & Lahav 1986) to measure accurately the macular surface area occupied by drusen. Analysis of serial photographs enabled us to follow the changes in the drusen area over time.

Patients and Methods

Subjects

All subjects were male patients seen at the Boston Veterans Administration Hospital's Retina Clinic. Photographic records of eyes of 122 patients (244 eyes) with a diagnosis of ARM were reviewed. Criteria for inclusion in the study were as follows: 1) drusen recognizable on fundus color slides, 2) absence of exudative complications of ARM, and 3) follow-up longer than 2 years.

Because drusen could not be identified reliably on some color transparencies, 102 eyes were excluded from the study. The reasons for exclusion were pigment epithelium changes without obvious drusen (40 eyes), media opacities (9 eyes), inadequate photographic documentation (16 eyes), and unclear diagnoses from fundus photographs or diagnoses other than ARM (37 eyes). We excluded 69 additional eyes because of exudative ARM: choroidal neovascular membranes (23 eyes), RPE detachment (6 eyes), and disciform scarring (40 eyes). Of the 73 remaining eyes, 48 eyes (27 patients) satisfied the follow-up requirement. We could obtain photographic follow-up for only 34 eyes of 20 patients; 12 eyes (9 patients) were ineligible for this study because exudative complications had developed in 8 eyes and media clarity had deteriorated greatly in 4 eyes. Therefore, 22 eyes (11 patients) with a follow-up longer than 2 years met the criteria for the study. Patient ages ranged from 54 to 91 years (mean, 66 years; median, 64.5 years).

Eyes were classified as containing predominantly hard or soft drusen. Hard drusen were defined as sharp-edged, yellowish-white, round and generally small subretinal deposits, approximately 50 μm in diameter; however, no measurement of size was taken. Soft drusen were defined as larger deposits with indistinct edges that appeared confluent. Baseline fundus photographs were used to classify the drusen as hard or soft by a single, masked observer. Four other independent observers (physicians and scientists) then classified the photographs according to the same criteria.

Technique

The computerized image-analysis technique has been described previously (Peli & Lahav 1986). Standard color transparencies (Ektachrome En 100 ASA, Eastman Kodak, Rochester, NY) were taken with a Zeiss FF3 fundus camera (Carl Zeiss, Thornwood, NY) and centered on the macula. Color slides were projected by a condenser photoenlarger through a green filter onto a linear-array digitizing camera (Datacopy, Mountain View, CA) and displayed on an image-display system (Adage, Billerica, MA). Digitized images of the macular areas containing the most drusen were stored on a computer disc. Each stored image had a standard size of 256 × 256 pixels and corresponded approximately to 2 × 2 vertical disc diameters (12° × 12°) at the magnification used. The drusen area was calculated in the arbitrary surface area unit, A; one [A] corresponded to 1% of the total area of the processed image, equaled 655 pixels, and corresponded to about 0.12 mm^2 on the retina.

The change in the drusen area was calculated in 3 ways: 1) the absolute change in the drusen area was the total change measured in pixels and expressed in units of [A], 2) the relative change represented the percentage of area change from the initial (baseline) area occupied by the drusen, and 3) the annual rate of (absolute) change was calculated in units of [A/year].

The images of each eye photographed at baseline (first set of photographs available) and follow-up were aligned. Using the adaptive thresholding technique (Peli & Lahav 1986), we converted the digitized image into a binary image. To reduce artifacts caused by vessels or pigment clumping, the operator used a bit-pad graphic input to delete manually erroneous thresholds assigned to these areas. This manual editing was done before the digitized image was converted into binary form. The number of points identified as drusen were calculated from the binary images. When multiple photographs taken during the same sitting of the same eye were available, the values were averaged.

Reproducibility

Reproducibility of the technique was assessed from multiple photographs of the same eye taken at the same sitting; these were available for 17 eyes. Multiple photographs were not available for the remaining 5 eyes. Two to three repeat photographs of the same eye taken at the same sitting were digitized, aligned, and processed as described earlier. The drusen area was calculated for each image. Reproducibility in percent was defined as the coefficient of variation (SD/mean) × 100. These

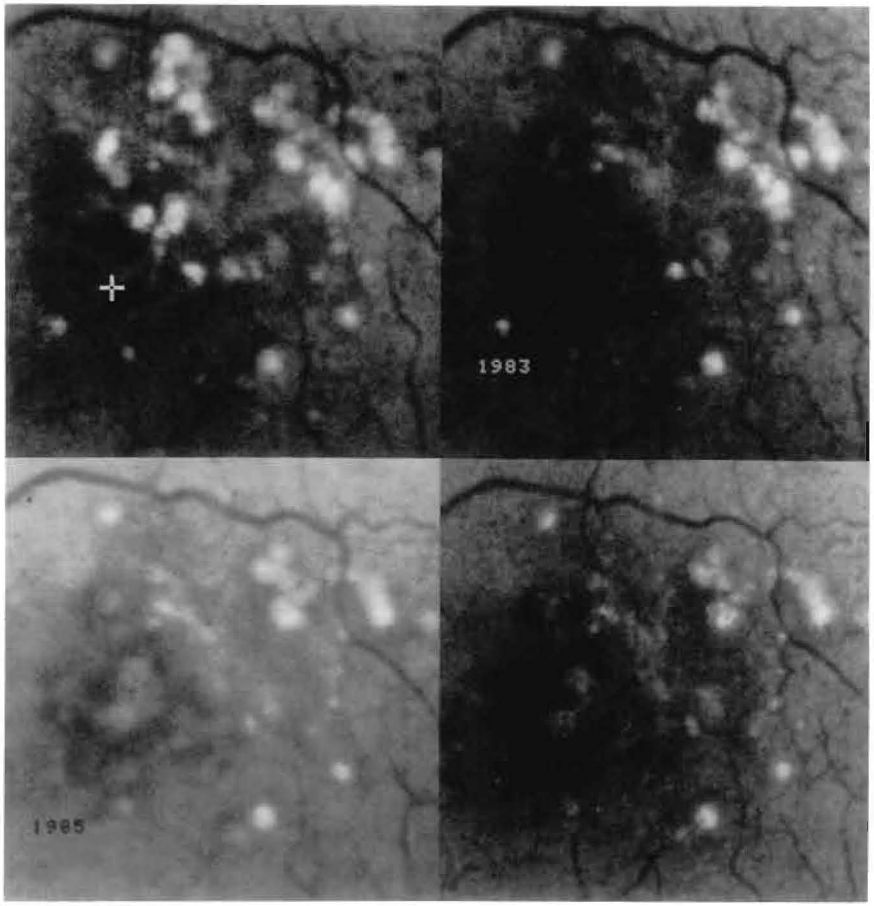

Fig. 1.
Changes in drusen pattern in a patient followed from 1980 (top left) through 1983 (top right), and from 1985 (bottom left) to 1987 (bottom right). Decrease in number and in size of drusen is visible in these macular photographs

Table 1.
Drusen changes in the study sample.

	Direction of change (follow-up: > 2 years)		Type of drusen	
	Increase	Decrease	Soft	Hard
No. of eyes	8	14	10	12 (NS)
Mean age at baseline* (years)	69.8	65.4 (NS)	64.6	69.0 (NS)
Mean follow-up (years)	4.2	4.9	5.1	4.5 (NS)
Mean drusen area at baseline* [A]	4.4	9.3[a]	10.4	5.1[a]
Mean relative change in drusen area (%)	+44.4	−53.8 (NS)	−49.5	+51.1 (NS)
Mean absolute change in drusen area [A]	+1.5	−4.9[b]	−5.6	+2.1 (NS)
Mean absolute rate of change [A/years]	+0.4	−1.2[c]	−1.4	+0.6[c]

[A] = arbitrary unit of surface area; NS = non-significant difference.
*Baseline is defined as the first set of photographs available for each eye. [a]$P < 0.001$. [b]$P < 0.02$. [c]$P < 0.05$.

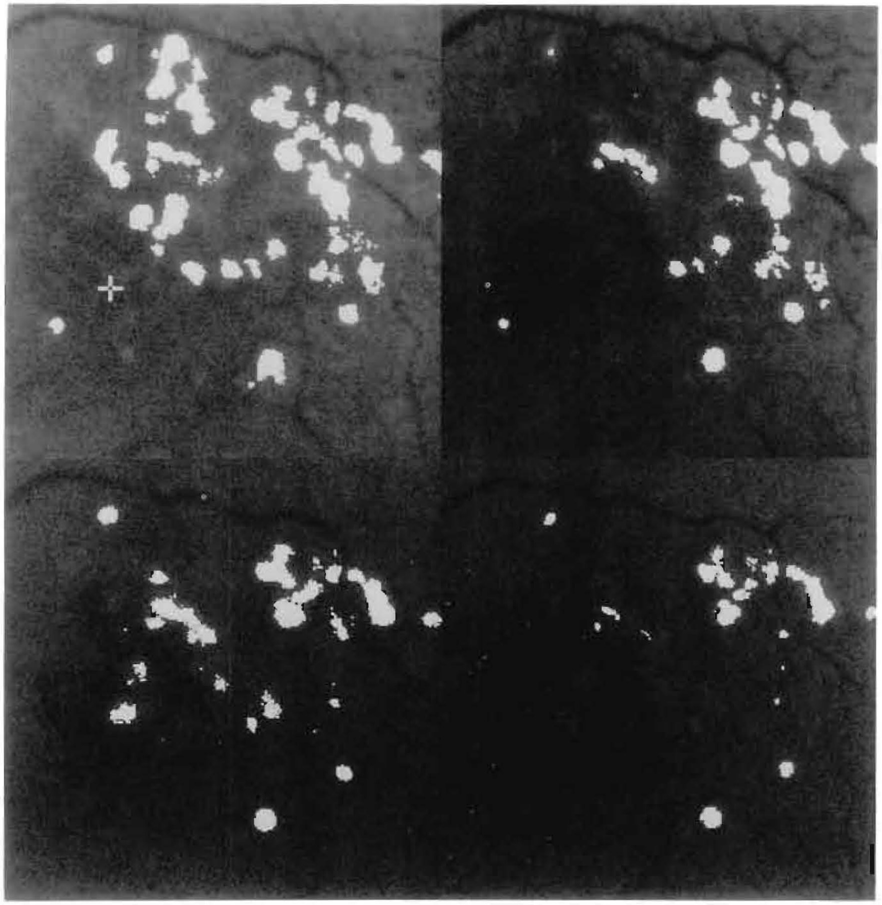

Fig. 2.
Results of drusen detection in the same fundus images as in Fig. 1. The areas detected as drusen are superimposed as white spots on original image.

values were calculated for each set, and reproducibility was averaged.

Results were analyzed statistically by the Student's *t*-test, linear regression analysis, and a non-parametric analysis using Fisher's exact probability test.

Results

The study findings differentiated by an increase or a decrease in the drusen area and by drusen type are summarized in Table 1. The patients studied averaged 66 years of age (mean) at baseline (range, 54 to 91 years; median, 64.5 years) and were followed for more than 2 years (mean, 4.7 years).

Reproducibility

The reproducibility (R) of the technique as assessed from photographic multiples of 17 eyes was R = 4.7 ± 3.5% (range, 0.8-14.3%), which agrees with the value of 6.1% provided by our pilot study (Peli & Lahav 1986).

Change in the drusen area

Relative change ≥ ± 20% of the baseline area was seen in 18/22 (82%) eyes. A change of ± 20% was a conservative definition of significant change, approximating the value of ± 18.7% (R + 4 SD).

The mean relative change in the drusen area (increase or decrease from initial value) was 50.6%. The mean absolute change in the drusen area was 3.7 [A]. The mean rate of change was 0.9 [A] per

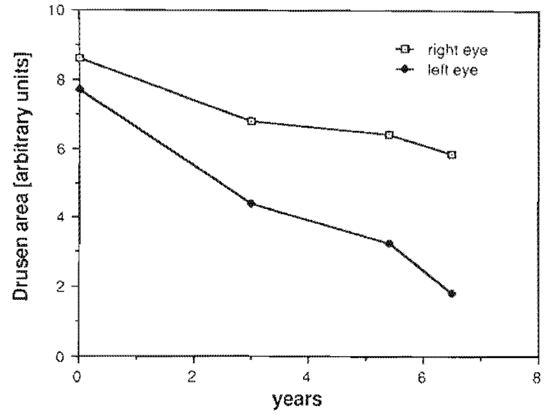

Fig. 3.
Change in absolute drusen area measured for eyes in Figs. 1 and 2.

year. Age at baseline did not correlate significantly with either relative change ($r = -0.05$) or absolute change in the drusen area ($r = -0.06$). Age and length of follow-up were similar for eyes with increased or decreased drusen area. The mean relative decrease in drusen area did not differ significantly from the mean increase in this area. The mean rate of decrease per year in the drusen area was significantly different from the mean rate of increase.

Figs. 1, 2 and 3 illustrate a steady decrease in the drusen area in a patient followed for more than 6.5 years.

Hard vs soft drusen

Ten eyes had soft drusen vs 12 with hard drusen. The agreement between the 4 independent observers in classifying the drusen was 88.2% (mean). Agreement between these 4 and the single, masked observer was 88.9%.

In all subjects, the predominant drusen type at baseline was identical in both eyes. The mean age and follow-up were similar for patients with hard and soft drusen. The mean drusen area at baseline was greater in eyes with soft drusen than with hard drusen.

Absolute and relative changes in the drusen area did not differ significantly between eyes with hard or soft drusen. However, the mean (absolute) rate of change for the soft-drusen eyes was significantly greater than that for the hard-drusen eyes (−1.4 vs +0.6).

Direction of change and type of drusen

Since large size was one of the criteria for classification of soft drusen, the baseline drusen area and the predominant type of drusen were not independent variables. Nonparametric analysis of the relationship between the direction of change and the type of drusen was performed. The direction of change in the drusen area was associated significantly with the predominant type of drusen at baseline, with soft-drusen eyes showing a decrease and hard-drusen eyes an increase. This was significant for all study eyes ($n = 22$, $P = 0.02$). Age younger or older than the median (64.5 years) was not associated significantly with the direction of change in all eyes.

Eye pairs

The relative change in the drusen area in 11 eye pairs was analyzed. The direction of change was bilateral in all patients: both eyes in all pairs showed a concomitant increase or decrease in the drusen area.

The mean relative change in the drusen area (increase or decrease) in eyes less affected by drusen (25.7%) was significantly less than that in fellow eyes (60.8%, $r = +0.86$, $P < 0.01$). The mean absolute change in the drusen area was greater in the more affected eye (4.4%) as opposed to the less affected eye in each patient (1.6%, $P < 0.05$). The mean absolute rate of change in the drusen area was also greater in the more affected eye (1.2 [A/year], $P < 0.05$).

Discussion

Measurement of the macular area affected by drusen permits direct monitoring of drusen changes. The computerized image-analysis technique used in this study is a reliable method for measuring the drusen surface area. The mean coefficient of variation was approximately 5% in both this study and an earlier pilot study (Peli & Lahav 1986). Using a partially computerized technique, Vidaurri et al. (1984) found that the mean surface area occupied by drusen in a 5° area centered on the fovea was 6.4%. This value approximated our finding of 11.0% for a 12° × 12° area.

Our results support the concept that drusen undergo a dynamic process, changing in surface area over time. This finding confirms previous qualitative clinical observations that drusen change in number and size over time, increasing (Sarks 1952, 1980; Gass 1973; Teeters & Bird 1973), decreasing (Bonnet et al. 1976; Sarks 1980), and sometimes disappearing (Sarks 1952; Frank et al. 1973; Gass 1973). Pearce (1968) and Deutman & Jansen (1970) reported a gradual increase, first in number and then in size, of drusen with increasing age. Bonnet et al. (1976) noted that a gradual decrease in the drusen area was sometimes preceded by confluence of smaller drusen into a larger mass. Teeters & Bird (1973) reported that 38% of 42 eyes with a mean follow-up of 1 year showed increased drusen and pigment epithelial defects without exudative complications. Gass (1973) found that 22 patients with bilateral drusen and a mean photographic follow-up of 5 years showed either an increase or decrease in drusen area, but 7 patients with a mean follow-up of 3 years showed no change.

A significant finding in our study was that the direction of change in any given eye correlated strongly with that in the fellow eye (which initially comprised the same type of drusen). We believe that this reflects a similar process of aging in both eyes afflicted with drusen. Although the direction of change was identical in both eyes, they differed significantly in the magnitude and rate of change. This unequal progression may relate to the clinically observed lag time in development of exudative complications in the eye when the fellow eye is affected by a disciform lesion (Gass 1973).

In our study, follow-up time was the single, most important determinant of the magnitude of relative change in drusen area. Taken singly, age, the initial drusen area, and the predominant type of drusen at baseline were not associated significantly with relative change in the drusen area. The drusen area change was significantly greater in eyes with longer follow-up. A greater drusen area change was also significantly associated with a larger baseline drusen area and predominance of soft drusen. The rates of absolute change in the drusen area were more than twice as great for soft-drusen vs hard-drusen eyes and for eyes with larger vs smaller baseline drusen areas. A decrease in drusen area was associated significantly with a larger baseline drusen area and predominance of soft drusen. In contrast, an increase was associated with an initially smaller drusen area and mostly hard drusen.

It is unclear whether all drusen start as the same type and undergo successive changes in size or drusen start as different types. Sarks (1980) believes that soft drusen progress or regress more rapidly, whereas hard drusen tend to enlarge slowly over many years (Sarks 1952). These concepts are supported by our results, which furthermore suggest that the disappearance rate of drusen is significantly faster than the growth rate.

An unexpected finding in our study was that all eyes with mostly soft drusen showed a decrease in the drusen area during the follow-up period. One possible explanation of this finding is that soft-drusen eyes underwent a phase of slow drusen growth followed by a phase of faster drusen loss. Alternatively, some individual drusen may have increased in surface area while the majority were decreasing. A third, less likely possibility is that by excluding eyes with exudative complications, we also may have excluded eyes with soft drusen that possibly increased in area.

The prognostic significance of change in the drusen area is controversial. A rapid increase in drusen number has been implicated as a poor prognostic sign of visual outcome (Sarks 1976; Strahlman et al. 1983) and has been associated with exudative complications. On the other hand, Gass (1973) found that fading of drusen frequently preceded geographic atrophy. Our results indicate that the most rapid phase is the fading of soft drusen, yet the effect on visual loss remains to be determined.

A review of the literature generally supports the idea that hard drusen are followed by soft drusen, which tend to disappear. In the general population, the prevalence of macular hard drusen is roughly twice that of soft drusen (Coffey & Brownstein 1986). In the population studied by Sarks (1976), the ratio of hard to soft drusen inverted gradually with increasing severity of nonexudative ARM. Coffey & Brownstein (1986) demonstrated a significant correlation between increasing age and soft but not hard drusen, which suggests that soft drusen appear later in life. Histologic studies have shown gradual softening of hard drusen (Sarks 1980; Sarks et al. 1980) as well as disappearance of soft drusen over time (Frank et al. 1973; Sarks 1980).

Based on our results, macular drusen appear to undergo a dynamic process with a predictable pattern of evolution. Hard drusen change slowly with a tendency to increase in surface area and to soften with time. Soft drusen appear later, possibly from softened hard drusen, and change more rapidly in surface area than do hard drusen. The eventual outcome of these changes is a subject for further studies.

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