Article

The Relationship Between Central Drusen Volume and Low-Luminance Deficit in Age-Related Macular Degeneration

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Purpose: To determine the relationship between central drusen volume and low-luminance deficit (LLD) in visual acuity (VA) in patients with intermediate age-related macular degeneration (AMD).

Methods: In this cross-sectional study, 42 patients with intermediate AMD underwent testing for VA and low-luminance VA (LLVA), as well as spectral-domain optical coherence tomography. LLD was calculated as the difference between VA and LLVA. Central drusen volume was measured in the central 3 mm of the macula, defined as the volume between the inner border of the retinal pigment epithelium and Bruch's membrane.

Results: Mean $\pm$ standard deviation (SD) LLD was 0.32 ± 0.12 logMAR and mean $\pm$ SD drusen volume was 0.18 ± 0.09 mm^3. No linear relationship was identified between central 3 mm drusen volume and LLD ($P = 0.215$). R^2 for the bivariate linear model was 0.038 (95% confidence interval 0–0.222). Limitation of the analysis to drusen volumes measured in the central 1 mm of the macula did not impact results ($R^2 = 0.075$), nor did incorporation of lens status into the model ($R^2 = 0.067$) or censoring of patients with nonfoveal subretinal drusenoid deposits ($R^2 = 0.071$).

Conclusions: The amount of drusen within the central 3 mm of the macula does not appear to be related to LLD in intermediate AMD. These measures may be manifestations of different underlying pathophysiological mechanisms.

Translational Relevance: Understanding relationships between markers for AMD progression may help guide development of improved clinical grading scales for AMD.

Introduction

Age-related macular degeneration (AMD) is a progressive, degenerative disease that is a leading cause of vision loss in the developed world.[1] It is estimated that 7% of the US population over the age of 40 years is affected.[2] The majority of vision loss in AMD is attributable to late stage disease, which is characterized by geographic atrophy (GA) of the outer retinal layers and/or choroidal neovascularization (neovascular AMD). At present treatment exists for the neovascular form but no therapies are available for individuals with GA.

Treatment for patients with early or intermediate stage "dry" AMD is also not available. This category of AMD patients presents with a wide spectrum of clinical and anatomic disease severities. Visual acuity (VA), the most commonly used measure of visual function, is often unaffected in early and intermediate stage disease.[3] To better stratify disease severity and risk of progression to more advanced disease, there is a need to identify additional markers for AMD progression and to understand the relationships between these markers.

Anatomic features have long been used to stage AMD. The presence of large (>125 μm diameter) drusen on color fundus photography is an established risk factor for the development of advanced AMD.[4] The exact role of drusen in the progression of AMD is complex, but studies have demonstrated that drusen are associated with photoreceptor thinning,[5,6] disruption of the ellipsoid zone,[7,8] and the appearance of

hyperreflective foci on spectral-domain optical coherence tomography (SD-OCT), a finding that is associated with the development of GA.[9,10] Recently, central drusen volume measured on SD-OCT has emerged as a potential marker for AMD severity, with several studies suggesting that central drusen volume is predictive of progression to both neovascular AMD and GA.[11–13] Drusen volume is attractive as an endpoint because it is easily measured, reproducible, and can be automated in commercially available SD-OCT software packages.

Functional alternatives to VA have also been explored as potential markers of AMD progression. Such alternatives would therefore be potentially useful as endpoints for treatment trials in intermediate AMD. These tests include low-luminance VA (LLVA), low-luminance deficit (LLD), fundus microperimetry, color contrast sensitivity, and dark adaptation.[3,14–16] Among these, LLVA and LLD are the most straightforward and could be easily incorporated into routine clinical trial workup, requiring only the addition of a neutral density filter to standard VA assessments. Difficulty with low-luminance visual tasks is a commonly reported symptom even in earlier stages of AMD[17,18] and may portend subsequent disease progression.[19] Several studies have shown that LLVA may be depressed in early and intermediate AMD when compared with normal controls.[14,20] LLD specifically has been associated with a higher risk of vision loss and lesion enlargement in patients with GA[21,22] and worse self-reported night vision symptoms in patients with intermediate AMD.[23]

Although drusen volume and LLD represent two somewhat divergent approaches to assessing AMD severity, it is plausible that they might be correlated or otherwise somehow related to each other. An understanding of these relationships is necessary if either or both of these parameters are to be utilized within clinical grading scales for AMD or as endpoints in clinical trials for dry AMD. Therefore the objective of the current study was to explore the relationship between LLD and drusen volume in a cohort of patients with intermediate AMD.

Methods

This cross-sectional study was conducted with the approval of the University of Texas Southwestern institutional review board (Dallas, TX). All study protocols were adherent to the tenets set forth in the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

Participants

Following written informed consent, patients with intermediate AMD (defined as the presence of at least one druse ≥ 125 μm in diameter on color fundus photography)[4] underwent examination at the Retina Foundation of the Southwest, Dallas, Texas, USA. All patients had the diagnosis of intermediate AMD confirmed by an experienced retina specialist (KGC). Additional inclusion criteria included age ≥ 55 years and VA of 20/63 (logarithm of the minimum angle of resolution [logMAR] of 0.50) or better.

Exclusion criteria included any evidence of active choroidal neovascularization or GA (foveal or nonfoveal) on SD-OCT, presence of any other vision-threatening retinal pathology, significant lens changes impairing ability to perform study examinations, lack of measurable soft drusen in the central 3 mm of the macula on SD-OCT, or evidence of subretinal drusenoid deposits (SDD) of >9 disc areas (DA) total or >0.25 DA within 1 mm of the fovea. SDD was assessed by a single grader (KGC) on fundus autofluorescence images or infrared reflectance imaging taken at the baseline visit, or within 6 months of the baseline visit. For patients with intermediate AMD in both eyes, the eye with better VA was designated as the study eye.

Study Examinations

Study examinations included VA testing under both normal and low-luminance conditions, SD-OCT, color fundus photography, and standard ophthalmic examination. VA testing was conducted prior to imaging studies to minimize bleaching of the retina.

VA Testing

VA was measured using an Early Treatment Diabetic Retinopathy Study chart at 4 m, with spectacle correction, at a luminance of 130 candela/m^2. Immediately following, LLVA was measured by placing a 2.0-log unit neutral density filter over the study eye and repeating the VA assessment. VA and LLVA were recorded in letters and converted to logMAR for analysis. LLD was calculated as the difference between VA and LLVA.

Imaging

SD-OCT was acquired using the Heidelberg Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany). Volume scans were obtained over a field spanning 15° horizontally and 10° vertically

Table.   Patient Demographics

Eye, n (%) OD	21 (50)
Age (years), mean (range)	75 (55–98)
Sex, n (%) female	28 (67)
VA (logMAR), mean (range)	0.13 (0.48 to –0.18)
Approximate Snellen equivalent, mean (range)	20/25 (20/63–20/12)
LLVA (logMAR), mean (range)	0.44 (0.96–0.10)
Approximate Snellen equivalent, mean (range)	20/50 (20/200–20/25)
LLD (letters), mean (range)	0.32 (0.14–0.60)
Central 3 mm drusen volume (mm^3), mean (range)	0.18 (0.11–0.54)
Central 1 mm drusen volume (mm^3), mean (range)	0.03 (0.01–0.10)
Nonfoveal SDD, n (%)	6 (14)

OD, oculus dextrus.

centered on the fovea and consisted of 97 horizontal B scans. Retinal layers were automatically segmented by the Heidelberg module. All segmented volume scans were reviewed by a grader (WCO, RAD, KGC), and any errors were manually corrected. Drusen volume was measured in the central 3 mm of the macula using the built-in functionality of the Heidelberg module. Drusen volumes for the central subfield (1 mm) of the macula were also recorded. Specifically, drusen volume was defined as the volume between Bruch's membrane and the inner border of the retinal pigment epithelium (RPE). SDD were not included in the segmentation of the RPE and did not contribute to drusen volume. Images were also assessed for the presence of absence of drusen in the central 1 mm, corresponding to the fovea.

Statistical Analysis

The first available visit per patient was selected for analysis. The relationship between drusen volume and LLD was analyzed using ordinary least squares regression. The confidence interval (CI) for the coefficient of determination (R^2) for this comparison was determined using simple quantiles derived from a bootstrap simulation. LLD was compared among phakic and pseudophakic eyes and among eyes with and without foveal drusen using the Student's *t*-test. Statistical analyses were conducted in R version 3.4.3 (R Project for Statistical Computing; www.r-project.org). A *P* value <0.05 was considered significant. All reported *P* values are two-sided.

Results

Forty-two patients with intermediate AMD were included in the study. Baseline demographics are shown
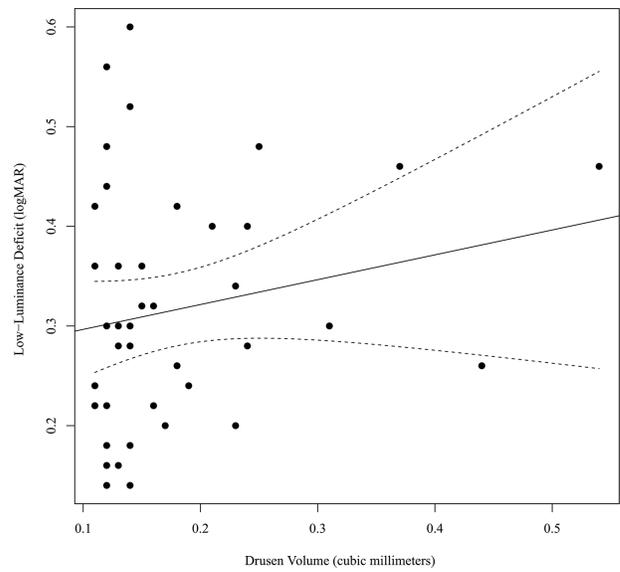

Figure 1.   Scatterplot of drusen volume (mm3) versus LLD. The bivariate linear regression line is plotted (*solid*) with the 95% CI for mean predicted values (*dashed*).

in the Table. Mean age was 75 years (range, 55–98 years), mean VA was 0.13 logMAR (approximate Snellen equivalent 20/25; range, 0.48 to –0.18 logMAR), mean ± standard deviation (SD) LLD was 0.32 ± 0.12 logMAR (range, 0.14–0.60 logMAR), mean ± SD 3 mm drusen volume was 0.18 ± 0.09 mm^3 (range, 0.11–0.54 mm^3), and mean ± SD 1 mm drusen volume was 0.03 ± 0.02 mm^3 (range, 0.01–0.10 mm^3). Six patients (14%) had nonfoveal SDD ranging from <1 to 9 DA, with LLD ranging from 0.22 to 0.60 logMAR.

Linear regression (Fig. 1) did not identify a significant relationship (n = 42, *P* = 0.215) between central 3 mm drusen volume and LLD (β = 0.025 logMAR/0.1 mm^3; 95% CI, –0.015 to 0.065 logMAR/0.1 mm^3). R^2 for the linear model was 0.038, and the 95% CI for R^2 as determined by bootstrap simulation was 0 to 0.222.
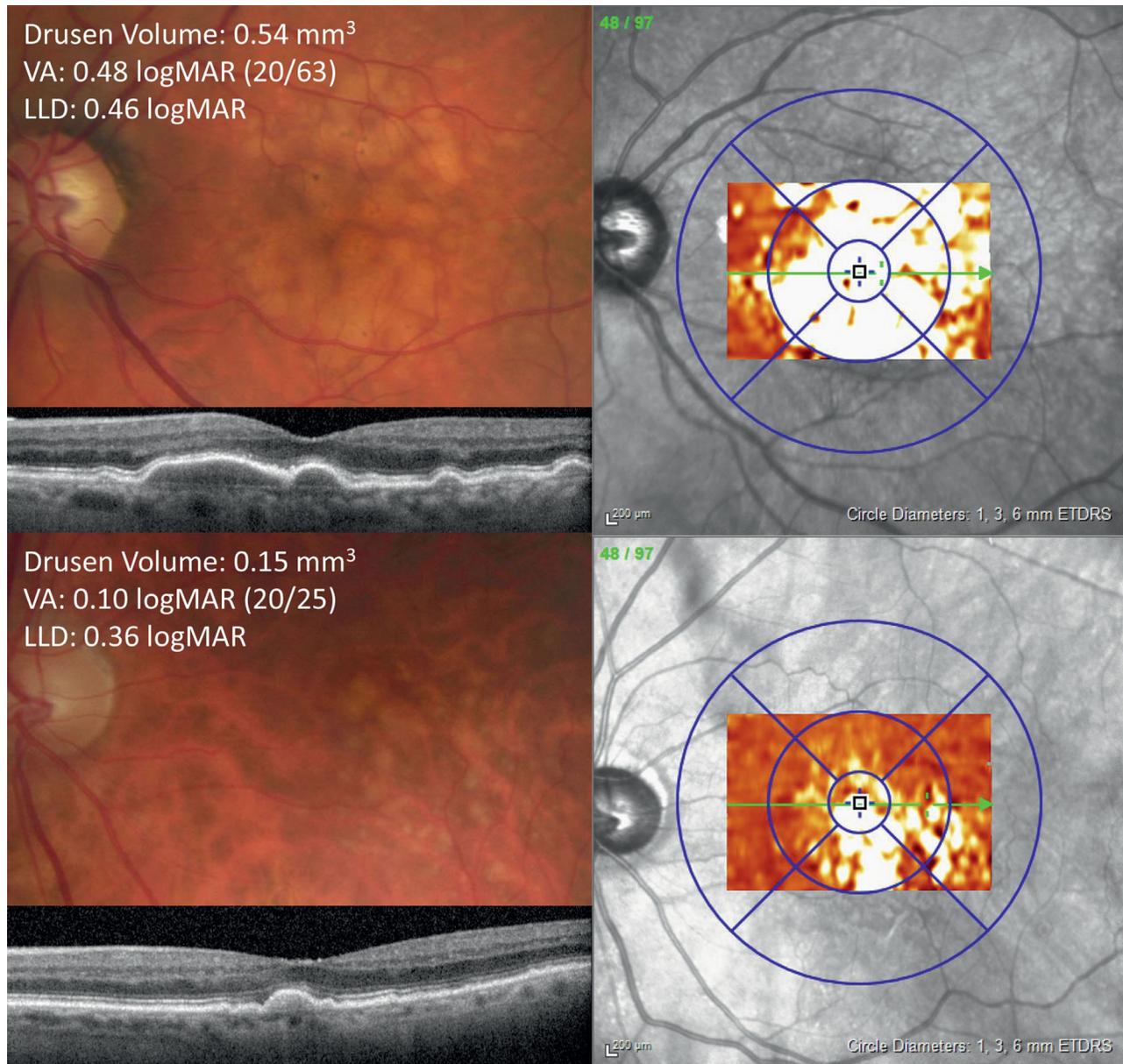
Figure 2. Color fundus photograph, optical coherence tomography (OCT) line scan, and drusen volume thickness maps for two patients (*top* and *bottom*) that both have a relatively high LLD despite a disparity in drusen volumes.

Results were similar when the analysis was repeated using central 1 mm drusen volumes (n = 42, β = 0.016 logMAR/0.01 mm^3, $P = 0.079$). R^2 for this model was 0.075. There was no significant difference in LLD between eyes with (n = 36, mean LLD 0.31 logMAR) and without (n = 6, mean LLD 0.33 logMAR) drusen in the central 1 mm of the macula ($P = 0.773$).

LLD was not significantly different between phakic (n = 20) and pseudophakic (n = 21) eyes ($P = 0.241$). Inclusion of lens status (phakic vs. pseudophakic) in the linear model for 3 mm drusen volume and LLD did not substantially impact the model (n = 41, β$_{drusen\ volume}$ = 0.023 logMAR/0.1 mm^3,

$P_{drusen\ volume}$ = 0.260), nor did censoring of six cases with nonfoveal SDD (n = 36, β = 0.030 logMAR/0.1 mm^3, $P = 0.117$). R^2 was 0.067 for the model including lens status and 0.071 for the model excluding patients with SDD. Representative case examples demonstrating the incongruity between drusen volume and LLD are shown in Figures 2 and 3.

Discussion

In this series, no significant linear relationship was identified between drusen volume and LLD, with
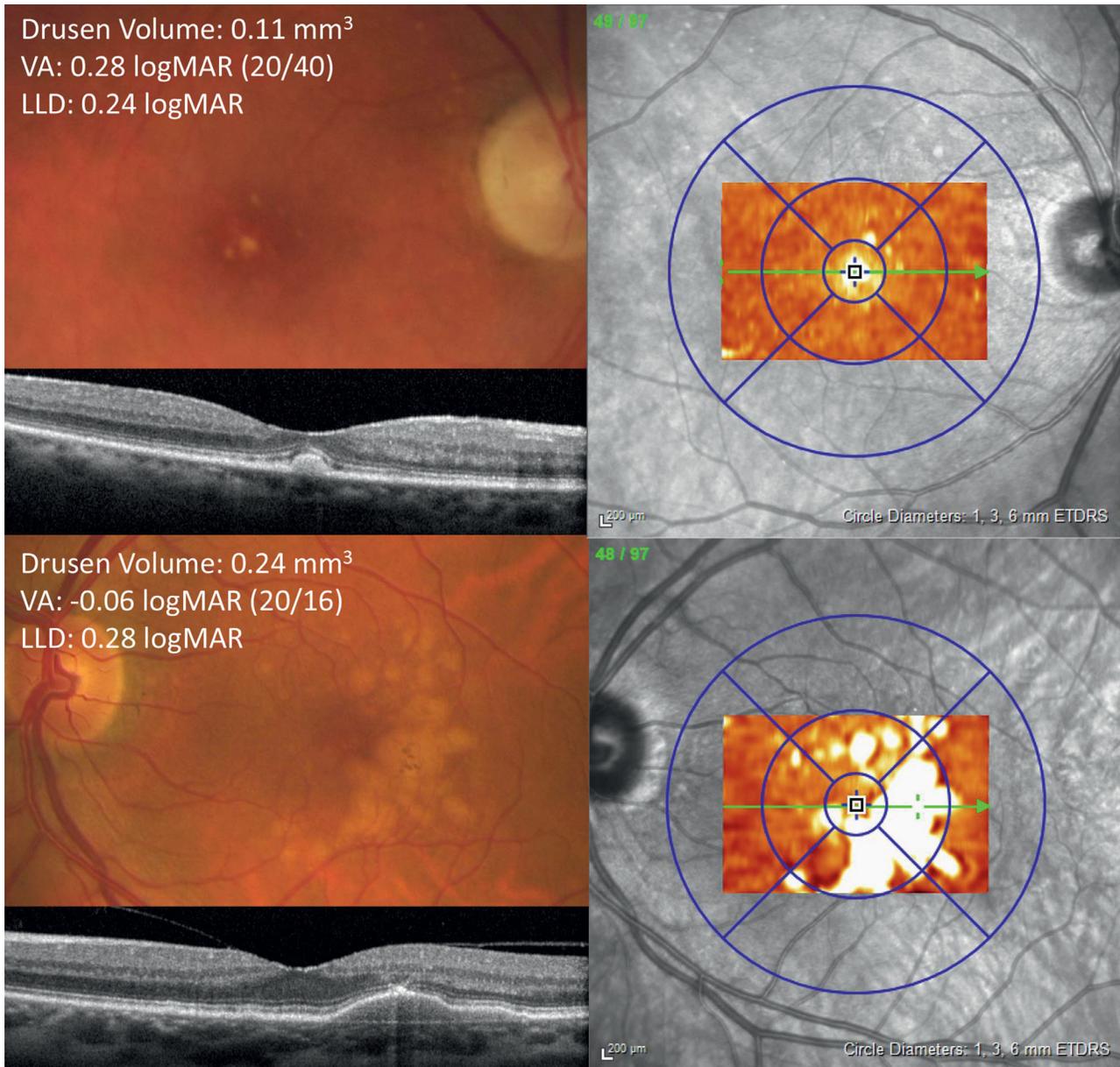
Figure 3. Color fundus photograph, optical coherence tomography (OCT) line scan, and drusen volume thickness maps for two patients (*top* and *bottom*) that both have a relatively small LLD despite a disparity in drusen volumes.

central 3 mm drusen volume accounting for only 4% of the variability in LLD (R^2). A bootstrap simulation, in which the sample data are resampled over a large number of iterations to generate a distribution for a statistic of interest, was used to generate a 95% CI for R^2. This simulation, assuming that subjects in the present sample are representative members of the population of interest (i.e., intermediate AMD patients), revealed a 95% CI of 0 to 0.222 for R^2. Thus although both drusen volume and LLD are thought to be markers of AMD severity, the current data suggests that the underlying processes reflected by these measures are not fully congruous.

Low-luminance, or mesopic, conditions represent a transition between rod-dominated scotopic vision and cone-dominated photopic vision during which both rods and cones contribute to visual function. However, their respective contributions are not simply additive, and the precise determinants of mesopic VA are incompletely understood. Modeling of mesopic vision is complicated by a number of factors, including differences in rod and cone sensitivities, interactions between rod and cone signaling, the existence of multiple postreceptoral pathways for signal processing, and different spatial distributions of rods and cones on the retina.[24] Rod-cone interactions are particularly

complex, involving direct cell–cell coupling through gap junctions, shared neural pathways, and temporal and phase interactions. Furthermore, rods appear to play a role in mediating cone survival.[25] Therefore although LLVA is generally considered a measure of cone function owing to the scarcity of rods in the fovea,[20,21] the potential contribution of rods to low-luminance dysfunction should not be overlooked, considering that rods are preferentially damaged before cones in AMD.[26]

Beyond the basic idea that drusen are indicators of an underlying disease process that may also manifest functional impairments such as LLD, there are several plausible links between drusen and retinal function. The presence of drusen has been associated with focal degenerative changes in the overlying photoreceptors, such as loss of photoreceptor density, outer segment thinning, and disruption of the ellipsoid zone as seen on both histological studies and on SD-OCT.[5–9,27,28] These changes may explain associations identified between drusen and retinal sensitivity deficits in early and intermediate AMD.[7,29–31] It follows that these same morphologic changes may impact LLD,[14] although the current study does not provide evidence to support this conclusion. Indeed, even when the analysis was restricted to the central 1 mm (i.e., fovea), in which one might anticipate the greatest degree of correlation with acuity, no significant relationship was identified between drusen volume and LLD. One potential contributor to the absence of an observed correlation in this study is the fact that drusen volume is not strictly unidirectional; that is, although drusen volume tends to increase over time, it is also known that drusen can shrink or disappear altogether, with the latter occurrence sometimes preceding progression to GA or neovascularization.[32] The inclusion of some patients who may have been in the midst of drusen regression despite being more advanced in their disease progression might explain the large range of LLD observed at low drusen volumes in this study.

Furthermore, it is likely that more than one mechanism contributes to LLD. Given the importance of rod-cone integration in mesopic vision, one hypothesis is that there may be pathologic postreceptoral changes in the inner retina, secondary to ischemia or photoreceptor damage, that affect visual function.[33,34] Another possibility is that thickening of Bruch's membrane in AMD may impair transport of vitamin A and impair photoreceptor kinetics.[26,35] It remains possible that other anatomic parameters, such as hyperreflective foci or assessment of ellipsoid zone integrity,[31,36] or other known markers of AMD severity, such as pigmentary abnormalities, may correlate more directly with LLD.

Further investigation of these potential associations may be revealing.

The authors have observed anecdotally that lens status may impact measurements of LLD, and cataract has previously been associated with poorer subjective low-luminance function.[37] In this study, no significant differences in LLD were identified between phakic and pseudophakic eyes, and inclusion of lens status in the linear model did not impact results. However, the amount of lens change in phakic eyes was not specifically assessed in this study.

Similarly, it has been suggested that the presence of SDD may impair low-luminance vision.[38] For this reason, patients with fovea-involving SDD or SDD >9 DA were excluded from the present study. However, six patients with SDD not meeting either of these exclusion criteria were included in analysis. Notably, censoring of these patients did not substantially impact the results of the regression analysis, and the risk of bias as a result of the inclusion of this small group of patients is likely low.

It is important to acknowledge that data regarding LLD in early and intermediate AMD have been mixed. In some series, LLD was found to be significantly worse in early and intermediate AMD patients compared with normal patients.[16,20] In contrast, Wu et al.[14] found that LLD in nonexudative AMD patients was significantly different from normal controls only in patients with nonfoveal GA. The same group later reported that baseline LLD was not correlated with 12-month changes in VA measures or microperimetric sensitivity, although changes in VA were minimal over this period.[15] Cocce et al.[3] found that LLD was significantly different between early and intermediate AMD patients, but only on computerized assessment. Although the utility of LLD in the classification of AMD remains unclear, it is likely still useful as a practical measure of patient functionality.[23]

A key consideration in assessing markers for intermediate AMD severity is risk of progression. A number of studies have demonstrated that increased central drusen volume is associated with progression to GA or neovascular AMD, and that above certain thresholds for drusen volume, the risk of progression greatly increases.[11–13] Although self-reported night vision symptoms have been associated with progression to GA or neovascularization,[19] it is currently unknown whether LLD specifically carries an increased risk of progression from intermediate to advanced AMD. The results of the current study suggest that if LLD does predict disease progression, it may do so independently of drusen volume.

This study has several limitations. First, the sample size is relatively small, and there are a limited number of observations available at higher drusen volumes. These points may therefore have had a disproportionate impact on regression analyses relative to other data points. Second, differences in methodology used to measure drusen volume in the present study may hinder comparison to previous studies on drusen volume. Specifically, the present study utilized Heidelberg SD-OCT images with drusen volume measurements made using the in-built functionality of the Heidelberg module. In contrast, many previous studies utilized Cirrus OCT (Carl Zeiss Meditec, Dublin, CA) with drusen volume measured using Cirrus software or custom software.[11–13,39] In the Cirrus module, drusen volume is based on the space between the segmented RPE and an interpolated "virtual" RPE containing no deformations,[40] whereas the Heidelberg module measures the space between the inner border of the RPE and Bruch's membrane. Although unlikely to have a substantial impact of the present results, these subtle differences in methodologies may hinder generalizability of the current findings.

Conclusions

There does not appear to be a relationship between drusen volume within the central 3 mm of the macula and LLD in the current series of 42 eyes with intermediate AMD. Instead, these two measures may be indicators of processes that independently contribute to disease progression.

Acknowledgments

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