Visual Function Measures in Early and Intermediate Age-Related Macular Degeneration

Arthika Chandramohan, MPH, **Sandra S. Stinnett, DrPH**, **John T. Petrowski, OD**, **Stefanie G. Schuman, MD**, **Cynthia A. Toth, MD**, **Scott W. Cousins, MD**, and **Eleonora M. Lad, MD, PhD**

Department of Ophthalmology, Duke University Medical Center. 2351 Erwin Rd, Durham, North Carolina 27705

Abstract

Purpose—The objectives of this study were to evaluate 1) the feasibility of performing computerized tests of low luminance visual acuity (LLVA), cone-specific contrast (CCT), contrast sensitivity, and microperimetry and 2) the test-retest repeatability of these outcomes in dry age-related macular degeneration (AMD).

Methods—This prospective study enrolled 30 subjects at a single site (8 controls, 8 early AMD and 12 intermediate AMD). Subjects underwent LLVA, contrast sensitivity, CCT, and microperimetry with eye tracking. Low luminance deficit (LLD) was defined as BCVA minus LLVA in EDTRS letters. Follow-up testing was administered at approximately one month.

Results—There was high test-retest repeatability at one month for all visual function metrics (intraclass correlations, ICC>0.7) except log contrast sensitivity (ICC 0.6). Compared to controls, patients with intermediate AMD showed significant deficits on BCVA, LLVA, LLD, percent reduced threshold on microperimetry, and red CCT (p<0.05), but not on contrast sensitivity, green and blue CCT.

Conclusions—This pilot study supports the feasibility and reliability of employing LLVA, microperimetry and CCT in early dry AMD. Our data suggests these measures can be employed as alternative future clinical trial endpoints. A larger prospective natural history study of alternative visual function measures in dry AMD is warranted.

Keywords

Age-Related Macular Degeneration; Visual Function Testing; Low Vision; Microperimetery; Low-Light Visual Acuity; Low Light Deficit; Contrast Sensitivity

INTRODUCTION

Age related macular degeneration (AMD) is the leading cause of severe central vision loss in the United States in people over the age of 50[1], affecting approximately 30% of individuals

Corresponding Author and Reprint Requests: Eleonora Lad, MD, PhD, Duke University Medical Center, Department of Ophthalmology – DUMC 3802, Durham, NC 27710. Telephone: (919) 684-0587; facsimile: (919) 681-6474; nora.lad@duke.edu.

over the age of 70 and 60 million people worldwide[2, 3]. The main risk factor for developing AMD is increasing age, as prior studies have shown that the prevalence of AMD more than triples for individuals aged 75-85 as compared to those aged 43-54[4]. With the projected increase in the aging population in the world[3], the impact of AMD on quality of life and medical cost is substantial[3, 5].

There are two forms of AMD: a "dry" and a "wet" form. The cause of vision loss in each is unique, though patients with the dry form may progress to the wet. In dry AMD, vision loss is associated with the formation of large drusenoid deposits in the macula, which ultimately result in photoreceptor degeneration, retinal pigment epithelium (RPE) atrophy and vision loss. The dry form accounts for approximately 85-90% of AMD cases[6]. In neovascular or "wet" AMD, vision loss is induced by onset of neovascularization with resulting subretinal fluid and hemorrhage leading to fibrosis and loss of central vision. Significant advances have been made in the treatment of wet AMD, especially with the introduction of safe and effective anti-VEGF agents[5, 7].

Despite its prevalence, no treatments exist for the majority of patients affected with its dry form. Because anatomic findings in dry AMD can be uncorrelated to progression or severity, the discovery of therapies for dry AMD is dependent on functional endpoints[8] as standardized biomarkers able to assess the severity, risk of progression, and response to treatment before significant visual changes occur[9]. Current monitoring relies on best-corrected visual acuity (BCVA), however visual acuity is not a sensitive functional measure until the late stages of disease. Alternatively, self-reported visual problems under low lighting and at night have been repeatedly documented in this group[10, 11].

Recent studies have shown that low luminance visual acuity (LLVA) is significantly reduced in early AMD[9, 12, 13]. In early AMD patients with intact BCVA, studies have documented impaired short wavelength cone function[14], reduced contrast sensitivity for central and peripheral vision[15, 16], and reduced retinal sensitivity as measured by standard microperimetry[12].

Thus, LLVA, cone-specific contrast, microperimetry, and contrast sensitivity are believed to be more sensitive to early macular changes than BCVA and may be potential endpoints for clinical trials of early dry AMD patients[12, 13, 16]. However, previous studies have been limited by a lack of comparability between all these testing measures. Herein, we aim to objectively compare these methods within a pilot study of normal controls, early AMD, and intermediate AMD patients. We demonstrate their feasibility and test-retest reliability, as well as suggest the most appropriate functional endpoints for clinical trials of early and intermediate AMD.

METHODS

Study participants

This prospective, controlled exploratory pilot study was approved by the Institutional Review Board of Duke University Medical Center and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Study subjects with AMD were identified from patients of the ophthalmology and optometry clinics at Duke Eye Center presenting for consultation. Spouses and friends of AMD subjects as well as Duke Eye Center optometry patients were recruited as control participants.

Inclusion criteria for study participants with AMD were capacity and willingness to provide consent, age >50 years, Snellen visual acuity of 20/40 (logarithm of the minimum angle of resolution, logMAR 0.30) or better, diagnosis of early (Age-Related Eye Disease Study, AREDS category 2) or intermediate (AREDS category 3) AMD[17] with presence of drusen larger than 63 μm and pigmentary anomalies. Drusenoid pigment epithelial detachments and non-foveal GA were allowed. Inclusion criteria for control subjects were identical for age and visual acuity, with no signs of AMD in either eye including reticular pseudodrusen, although fewer than 10 drusen ≤63 μm were allowed.

Individuals were excluded if they demonstrated any ocular abnormality other than AMD or cataracts, in addition to not being able to perform any of the designated tests or complete the consent form for other health reasons. When both eyes met the inclusion criteria, the eye with better visual acuity was chosen as the study eye or the following algorithm was used if both had the same visual acuity: odd birth month – OD and even birth month – OS.

Functional testing

Visual acuity evaluation and all functional tests were performed before fundus imaging to prevent bleaching of the retina. Subjects wore their best correction for all tests. BCVA was assessed via the Electronic Visual Acuity tester (EVA; JAEB Center, Tampa FL)[18] under photopic conditions (100 cd/m^2) and expressed in number of letters read. The tester runs the visual acuity testing program E-ETDRS (Electronic Early Treatment of Diabetic Retinopathy) that provides a visual acuity letter score comparable to the standard ETDRS chart testing score with additional benefits of electronic data capture and single distance testing from Snellen 20/12 to 20/800 range, as well as reduced testing time and technician-related bias[18, 19]. Testing began with a screening phase to determine the approximate visual acuity threshold. This phase was followed by threshold testing to determine an upper acuity level at which 5 of 5 letters were correctly identified and a lower level at which 0 of 5 letters were correctly identified. A letter score to approximate the standard ETDRS score was computed as the number of letters correctly identified during threshold testing at the most difficult level, plus 5 letters for each acuity line above the upper boundary through 20/800. Testing was conducted in the same room with dim incandescent lighting for all patients across visits and monitor luminance for BCVA testing was 85-105 cd/m^2 with a contrast of 98%.

LLVA, Cone Contrast Test (CCT), and contrast sensitivity testing were performed monocularly at near distance (1 m) using computerized tests developed by Innova Systems (Burr Ridge, IL). During the LLVA test, subjects were presented with a succession of lines composed of 5 Snellen letters of decreasing size on a PC computer (Dell Optiplex 9010) screen with the initial background luminance of 16 cd/m^2 followed by a different set of Snellen lines on a background with luminance of 5 cd/m^2. The resulting BCVA and LLVA in

Snellen letters were recorded and converted to ETDRS letters[20]. Low-luminance deficit (LLD) was calculated by subtracting LLVA from BCVA.

Next, subjects underwent CCT assessment, a computerized method of quantifying color vision and deficits in cone color discrimination at the photoreceptor level[21]. The test was conducted in a dark room while wearing best correction. Following instruction and demonstration with L, M and S letter appearance, the CCT presents a randomized series of colored letters visible to a single cone type (long L, medium M, or short S wavelength photoreceptors) in decreasing steps of cone contrast to determine the threshold for letter recognition. These cone scores are logarithmically normalized to a 100-point scale, 100 being the maximum score achievable[21].

Following CCT, a computerized contrast sensitivity test was performed. This is a rapid self-test measuring low contrast threshold by using low contrast letters on a white background. A staircase method is used to reduce contrast level to at or near threshold. Results are displayed in log contrast scores ranging from 2.0 log contrast (normal) to 1.0 log contrast (visual disability requiring 10 times as much contrast as compared to a person with normal contrast sensitivity).

Lastly, microperimetry testing was administered following pupillary dilation with one drop of tropicamide 1% and phenylephrine 2.5% each. Retinal sensitivity assessment was performed using a microperimeter with eye tracking (Macular Integrity Assessment MAIA; CenterVue, San Jose, CA)[9]. Subjects underwent a two-minute microperimetry training session to demonstrate the principles of the MAIA exam prior to the full test. This brief training exam is generally used before all MAIA testing sessions to familiarize the patient with the MAIA testing environment. The grid used during the full examination was designed to evaluate the macular region and consists of 37 points arranged in concentric circles and located at the fovea and 1, 3, and 5 degrees from fixation (Figure 2). Three microperimetry measures were derived: average threshold, percent-reduced threshold (PRT) and central retinal sensitivity (CRS). Average threshold is the average of all retinal sensitivities from all loci tested while CRS is the average of only the foveal locus and 12 points located at 1 degree from fixation. PRT is a derived functional index representing the percentage of measured thresholds below 25 dB.

In all study participants, functional measurements were repeated on a separate visit at approximately 1 month (+/- 10 days) from the initial visit to determine test-retest repeatability. This interval was chosen because no significant changes in disease progression or ocular health are expected, and most subjects were not able to return sooner for a follow-up study appointment which was not a standard of care examination. No patients were lost to follow-up during the duration of the study.

Imaging

Fundus imaging included color fundus photography (Zeiss FF 450 Plus IR, Carl Zeiss Meditec Inc., Dublin, CA) and fundus autofluorescence (Spectralis 3-mode, Heidelberg Engineering US, Carlsbad, CA). Spectral-domain optical coherence tomography (SD-OCT) scans were performed on a Spectralis OCT (Spectralis 6-mode, Heidelberg Engineering US,

Carlsbad, CA). Two retinal specialists (EML and CT) performed all clinical examinations. Color fundus photographs were graded by a medical retinal specialist (EML) by evaluating extent of pigmentary changes and drusen size[17]. Early AMD (AREDS category 2) was defined by the presence of many small drusen, few intermediate drusen, and/or RPE abnormalities, whereas intermediate AMD (AREDS category 3) was defined by extensive intermediate drusen, at least one large drusen and/or the presence of non-foveal geographic atrophy[17]. Fundus autofluorescence and SD-OCT images were used to confirm the color fundus grading.

Statistical Analysis

Descriptive statistics for functional measures were computed for all groups. Comparisons between groups were assessed using the Wilcoxon rank sum test of difference between medians; a correction was performed to account for multiple comparisons. Linear regression analysis was conducted to examine the relationship between different functional measures. The correlation coefficient R was computed to measure the strength and direction of the linear relationship between two variables.

The intersession test-retest repeatability of visual acuity and other functional measures was determined by calculating intraclass correlations (ICC) with 95% confidence intervals as well as with the coefficients of repeatability (CoR). The ICC represents the ratio of variance between subjects and the total variance, and best demonstrates quantifiable reproducibility. We employed the Bland-Altman analysis and plots (not shown) and calculated the coefficient of repeatability (CoR) related to the plots. The CoR, also referred to as the Smallest Real Difference[22], is an index that quantifies absolute reliability measurement error. If the differences between two measurements made on a subject are approximately normally distributed, we expect the absolute difference between two measurements on a subject to differ by no more than the CoR on 95% of occasions. The value of the CoR depends on the values of each measurement. The relationship between ICC and CoR is demonstrated below:

$$ICC = \frac{Between\,subject\,variance}{Between\,subject\,variance\,+\,within\,subject\,variance}$$
$$CoR = 1.96 \times \sqrt{2} \times Standard\,Error\,of\,the\,Mean\,(SEM)$$
$$SEM = \sqrt{within\,subject\,variance} - \sqrt{total\,variance}$$

The CoR of a tool is directly related to the 95% limits of agreement proposed by Bland and Altman[23, 24] and demonstrates the precision of measured values between initial and follow-up visits[25]. All statistical analyses for this paper were performed in SAS version 9.3 (SAS Institute, Cary NC).

RESULTS

A total of 30 participants were enrolled in the study (20 AMD subjects and 10 healthy controls) and underwent visual function testing on the same study eye at approximately 1 month (+/- 10 days) following the baseline examination. Of the subjects with AMD, 8 had the diagnosis of AREDS Stage 2 (early AMD) and 12 were characterized with AREDS

Stage 3 (intermediate AMD). Demographic characteristics and lens status are presented in Table 1; there was no overall significant intergroup variation with respect to age, gender, visual acuity or cataract status. Average age for control subjects was 69.2 ± 8.6 years, 67.5 ± 7.58 years for the early AMD group and 71.8 ± 6.8 years for the intermediate AMD group. Gender distributions (percent male) ranged from 58.3% in the intermediate AMD group to 62.5% in the early AMD group, (p = 1.00). The range of visual acuities was Snellen 20/13-20/25 for the control group, 20/13-20/40 for the early AMD group and 20/16-20/40 for the intermediate AMD group (Table 1 and Figure 1; p-value overall 0.112, however p-value between control and intermediate group was 0.029). Proportion of phakic subjects present among groups did not differ (Fisher's exact test p = 0.448). Pseudophakia was documented in one control patient, one early AMD patient, and 4 intermediate AMD patients.

Test-Retest Variability

To examine test-retest variability between the two testing sessions, ICC and CoR were calculated both amongst all patients as well within each study group (Table 2). Amongst all subjects, LLVA and LLD demonstrated ICCs of 0.86 and 0.87, respectively. Microperimetry measure ICCs ranged from 0.73 to 0.90 (Table 2), with average threshold exhibiting the highest of all overall ICCs at 0.90. All CCT measures (red, blue, green) had ICCs of ≥0.75. Red color testing on CCT demonstrated the best ICC at 0.83, followed by blue (0.79) and green (0.75) color testing. Log Contrast test exhibited the least substantial agreement (ICC 0.60).

Within individual comparison and control groups, each test's ICC measures displayed greater variability than overall ICC. The control group demonstrated a weaker array of ICCs (Table 2). Amongst patient groups, the intermediate AMD group paralleled the aggregate measures most closely, where log contrast sensitivity had the lowest ICC (0.71). Similar ICC trends were maintained within the early AMD group, with the exception of blue and green CCT, which displayed a low ICC in this population (<0.4). Red CCT, low luminance and microperimetry measures were characterized by ICC>0.7, with microperimetry's average threshold being the highest (0.96) (Table 2).

Functional Measures between groups

The functional measures that showed significant differences among all groups were BCVA, LLVA, LLD, red CCT and PRT on microperimetry testing (Figure 1). BCVA performance at baseline was similar between control and early groups but significantly lower in the intermediate AMD group as compared to controls. Significant differences were noted between early AMD and controls as well as between intermediate AMD and control groups for LLVA and LLD during at least one of the two visits (p<0.05; Figure 1). Red CCT also demonstrated a statistically significant difference between these groups within visit 2 (p = 0.020), though not at visit 1 (p = 0.115).

Microperimetry deficits varied within each clinical severity group. Specifically, PRT showed differences between control and intermediate AMD groups at visit 2 only (p=0.055). Figure 2 demonstrates a typical microperimetry examination in the three groups (control, early

AMD and intermediate AMD) as exemplified by three representative subjects, as well as the corresponding functional measures.

Correlations between functional measures

Bivariate fit analysis evidenced significant correlations between LLD and BCVA (R = -0.71, slope -0.75, p<0.001) among all groups, as well as between LLVA and BCVA, LLD, PRT, and central foveal sensitivity, respectively (Figure 3A-E). The strength of correlations between these variables differed within early and intermediate AMD groups. Analysis of the early AMD group showed a significant correlation only between LLD and BCVA, LLVA and BCVA, and LLVA and LLD (R = -0.88, 0.75, and -0.84 respectively). All significant correlations demonstrated using aggregate data (Figure 3) were present within the intermediate group analysis alone (R > 0.8), except for the correlation between LLD and BCVA, which was demonstrated between early and control groups (R = -0.88).

DISCUSSION

As researchers work to develop new treatments for dry AMD, they will require reliable and effective functional outcome measures. Recent studies have suggested a variety of alternative early endpoints[8, 26, 27], though all measures warranted further testing to establish accuracy, precision, and applicability to drug discovery and early functional disparities. Few studies have addressed the feasibility of implementing these tests in the clinical setting and their intrasession variability[28, 29], thus our goal was to address this gap and objectively examine feasibility and test-retest reliability.

The psychophysical tests employed in our study: LLVA, MAIA microperimetry, CCT and cone contrast sensitivity, captured a broad expression of AMD-related deficiencies. LLVA is a quick, reproducible measure of central cone-mediated function under conditions of reduced illumination, and can serve as a predictor of risk of vision loss even in eyes with normal BCVA[13]. Utilizing a computerized LLVA method allowed standardization of background luminance and testing conditions across various clinics, minimizing operator and patient-related factors (such as variability in angle and distance between the filter and the subject's eye, sight around the filter, difficulties holding the filter, etc.) and enabled multiple testing such as BCVA, CCT, and LLVA via the same interface. Retinal sensitivity as determined by MAIA microperimetry has recently been shown to detect a greater extent of foveal dysfunction than BCVA and standard LLVA, while also providing topographic information about functional defects[9]. The CCT is unique in its ability to accurately indicate the type and severity of color deficiencies as well as disease progression even in individuals with normal visual acuity[21, 30].

In our study, we found that computerized LLVA and LLD, CCT and MAIA microperimetry all demonstrated significant test-retest reliability (ICC >0.7). Wu et al. recently demonstrated similarly good intra-session test-retest reliability for MAIA microperimetry[28], however they also reported a "learning effect" influencing mean sensitivity between the first two MAIA administrations. Although there appeared to be a trend across groups towards improved PRT during the second visit, this effect was not reflected in ICC measures in our study, nor was it replicated in other previous studies[23, 31, 32]. In addition to using different

testing parameters, the patients enrolled in our study underwent a brief training session before the first examination, which likely reduced any learning effect during the first visit[28].

The CoRs obtained in our study for LLVA (9.34) and LLD (6.27) were similar to prior studies (0.13 log MAR or 6.5 ETDRS letters in the study of Wu and colleagues[28]). The CoR for the microperimetry measure CRS (+/- 4.27 dB) was comparable to findings from previous studies of +/- 4.76 dB reported by Wu and collaborators for pointwise sensitivities with MAIA microperimetry[28] and +/-5.56 dB documented by Chen and colleagues[32] using MP-1. The higher CoR obtained by Chen et al[32] with the Nidek MP-1 may be attributed to a greater number of stimuli tested (68 vs 37 used by Wu et al and our study), although this also significantly lengthens test duration. The CoR for average threshold in our study was more favorable than in all prior studies at 2.78 dB.

In the current study, only contrast sensitivity testing demonstrated lower inter-session reliability (ICC 0.6). This may be related to the variability of nuclear sclerotic cataract in our study population. The potential difficulty of this computerized test is its reliance on subject attention and familiarity with the test. Unlike microperimetry and the CCT test, this psychophysical test did not begin with a training session. Future studies should be performed using either the current methodology with an added training test or the Spaeth/Richman Contrast Sensitivity test—an internet-based method of testing contrast sensitivity that was recently demonstrated to be valuable for evaluating contrast sensitivity in AMD[15]. An additional limitation of our study was that all patients received the same order of testing across visits. This non-randomized administration may have influenced performance and inter-test variability due to order effects or fatigue. A future larger study in which testing order is randomized and perhaps repeated in a reverse order at follow-up is warranted. However, the consistent order of tests performed between visits in this pilot study created parallel testing conditions where such effects would be present in both visits and minimally affect test-retest reliability of a single test.

Another limitation of our pilot study was that the control group may have included some patients with AREDS category 1 since fewer than 10 drusen <63 microns were allowed. The decision to tolerate <10 small drusen in our control group is consistent with criteria employed by prior natural history studies[9, 12] and based on the current recommendations on clinical classification of AMD versus controls[17]. A future larger, longitudinal natural history study specifying strict inclusion criteria for the study groups is needed. This study should recruit subjects with good, intermediate and poor visual acuities in order to assess alternative visual function outcomes in the patients with a range of disease severity and visual acuities.

Although the main goal of our pilot study was to evaluate test-retest repeatability for the functional endpoints across all subjects, we noted significant differences between the intermediate AMD group and age-matched controls in BCVA, LLVA, LLD, CCT red and microperimetry PRT. Our findings were consistent with previous studies[9,33], in which intermediate stage patients demonstrated significantly worse LLVA and BCVA. A cone-mediated mechanism of low luminance deficit in early AMD suggests that LLVA testing may better capture nuanced functional deficits[13, 34, 35]. LLD has also been shown to strongly predict subsequent visual acuity loss at all levels of baseline visual acuity[13].

We also found a significant increase in LLD in both early and intermediate AMD groups as compared to controls during at least one of the two visits. Although a prior study found a difference in LLD between early stage AMD (defined by the presence of intermediate-large drusen ±RPE abnormalities) and controls[35], others found no significant difference between non-neovascular AMD groups and controls except for those with non-foveal GA[9]. However, in this prior work, 20% of participants with their definition of early AMD had a LLD worse by 2 SD as compared to normal, suggesting that LLD may indeed identify individual AMD eyes at risk for vision loss.

Our findings of a red cone contrast deficit in both AMD groups compared to healthy controls differed from an earlier study demonstrating blue color impairments in early AMD[14], and another documenting function deficiencies in all three types of photoreceptors[26]. This discrepancy may be explained by the small sample size of our study, or by the presence of lens opacification in some of the subjects as pseudophakic cases were concentrated in our study's intermediate AMD group, while controls had the majority of patients with ≥2+ NS. Indeed, earlier work has noted that the blue stimulus has good reproducibility but only moderate specificity, and testing performance along the blue-yellow axis is significantly impacted by the presence of cataract[36]. Our AMD groups had a lower cataract burden than controls, which may have decreased their blue contrast test performance to the degree of AMD patients. Further studies enrolling subjects with pseudophakia or non-visually significant cataract are required to understand the functional differences in all photoreceptor types between normal, early and intermediate AMD cohorts over time.

In the intermediate AMD group as compared to normal subjects, we also noted a significant difference only in MAIA microperimetry measures of PRT. In contrast, earlier work demonstrated significant reduction in CRS in a subset of intermediate AMD patients with large drusen and non-foveal GA, but not in subjects with early or intermediate AMD characterized by intermediate drusen[9]. Our small sample size precluded this type of subset analysis, however, our results suggest that PRT may be a superior microperimetry indicator of early dysfunction by distinguishing local sensitivity changes associated with focal pathology in early AMD.

Another important goal of our study was to examine correlations between visual function endpoints to assess possible surrogate markers of functional decline. All microperimetry indices appropriately correlated with one another, further emphasizing consistent measurements across this testing modality. The strong correlations between CRS and PRT with LLVA suggest that LLVA may be able to translate subtle changes in foveal pathology to a functional deficit. Nevertheless, others warned that LLVA might be limited in its ability to assess retinal function outside of the fovea, where the loss of function and atrophic changes occur first[37-39]. Yet in this pilot study, both early and intermediate groups demonstrated lower LLVA than control populations, supporting LLVA as a sensitive functional marker of early AMD.

In summary, our study supports the feasibility of employing computerized low luminance testing (LLVA and LLD), CCT and MAIA microperimetry in subjects with early and intermediate AMD. These tests were well tolerated and had high test-retest reliability in this

population. Our data suggest that this battery of psychophysical measures, in addition to other promising tests such as dark adaptation[40], may be employed as alternative early endpoints for future interventions in dry AMD. A larger prospective study fully investigating the natural history of these functional endpoints in early and intermediate AMD is warranted.

Acknowledgments

References

1. Bressler NM, Bressler SB. Preventative ophthalmology. Age-related macular degeneration. Ophthalmology. 1995; 102:1206–1211. [PubMed: 9097748]

2. Klein R, Klein BE. The prevalence of age-related eye diseases and visual impairment in aging: current estimates. Investigative ophthalmology & visual science. 2013; 54:Orsf5–orsf13. [PubMed: 24335069]

3. Rein DB, et al. Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. Archives of ophthalmology (Chicago, Ill : 1960). 2009; 127:533–540.

4. Klein R, Klein BE, Moss SE. Diabetes, hyperglycemia, and age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. 1992; 99:1527–1534. [PubMed: 1454318]

5. Malek G, Lad EM. Emerging roles for nuclear receptors in the pathogenesis of age-related macular degeneration. Cellular and molecular life sciences : CMLS. 2014; 71:4617–4636. [PubMed: 25156067]

6. Seddon, J. Epidemiology of age-related macular degeneration. In: Schachat, A., editor. Retina. Philadelphia, Pa: St. Louis: Mosby; 2001. p. 1039-1050.

7. Kovach JL, et al. Anti-VEGF Treatment Strategies for Wet AMD. Journal of ophthalmology. 2012; 2012:786870. [PubMed: 22523653]

8. Lesmes LA, Jackson ML, Bex P. Visual function endpoints to enable dry AMD clinical trials. Drug Discovery Today: Therapeutic Strategies. 2013

9. Wu Z, et al. Low-luminance visual acuity and microperimetry in age-related macular degeneration. Ophthalmology. 2014; 121:1612–1619. [PubMed: 24661863]

10. Owsley C, et al. Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. Invest Ophthalmol Vis Sci. 2006; 47:528–535. [PubMed: 16431946]

11. Steinmetz RL, et al. Symptomatic abnormalities of dark adaptation in patients with age-related Bruch's membrane change. The British journal of ophthalmology. 1993; 77:549–554. [PubMed: 8218049]

12. Wu Z, et al. Longitudinal changes in microperimetry and low luminance visual acuity in age-related macular degeneration. JAMA ophthalmology. 2015; 133:442–448. [PubMed: 25632841]

13. Sunness JS, et al. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. Ophthalmology. 2008; 115:1480–1488. 1488.e1481–1482. [PubMed: 18486216]

14. Holz FG, et al. Colour contrast sensitivity in patients with age-related Bruch's membrane changes. German journal of ophthalmology. 1995; 4:336–341. [PubMed: 8751098]

15. Faria BM, et al. Evaluating contrast sensitivity in age-related macular degeneration using a novel computer-based test, the spaeth/richman contrast sensitivity test. Retina. 2015; 35:1465–1473. [PubMed: 25658175]

16. Sunness JS, et al. Visual Function Abnormalities and Prognosis in Eyes with Age-related Geographic Atrophy of the Macula and Good Visual Acuity. Ophthalmology. 1997; 104:1677–1691. [PubMed: 9331210]

17. Ferris FL 3rd, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013; 120:844–851. [PubMed: 23332590]

18. Beck RW, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. American journal of ophthalmology. 2003; 135:194–205. [PubMed: 12566024]

19. Moke PS, et al. Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol. American journal of ophthalmology. 2001; 132:903–909. [PubMed: 11730656]

20. Gregori, NZ.; Feuer, W.; Rosenfeld, PJ. Retina. Vol. 30. Philadelphia, Pa: 2010. Novel method for analyzing snellen visual acuity measurements; p. 1046-1050.

21. Rabin J, Gooch J, Ivan D. Rapid quantification of color vision: the cone contrast test. Invest Ophthalmol Vis Sci. 2011; 52:816–820. [PubMed: 21051721]

22. Beckerman H, et al. Smallest real difference, a link between reproducibility and responsiveness. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2001; 10:571–578.

23. Weingessel B, et al. Interexaminer and intraexaminer reliability of the microperimeter MP-1. Eye (London, England). 2009; 23:1052–1058.

24. Bunce C. Correlation, agreement, and Bland-Altman analysis: statistical analysis of method comparison studies. American journal of ophthalmology. 2009; 148:4–6. [PubMed: 19540984]

25. McAlinden C, Khadka J, Pesudovs K. Statistical methods for conducting agreement (comparison of clinical tests) and precision (repeatability or reproducibility) studies in optometry and ophthalmology. Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists). 2011; 31:330–338. [PubMed: 21615445]

26. Neelam K, et al. Psychophysical function in age-related maculopathy. Survey of ophthalmology. 2009; 54:167–210. [PubMed: 19298899]

27. Hogg RE, Chakravarthy U. Visual function and dysfunction in early and late age-related maculopathy. Progress in retinal and eye research. 2006; 25:249–276. [PubMed: 16580242]

28. Wu Z, et al. Intrasession test-retest variability of microperimetry in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2013; 54:7378–7385. [PubMed: 24135753]

29. Haegerstrom-Portnoy G, et al. The SKILL Card. An acuity test of reduced luminance and contrast. Smith-Kettlewell Institute Low Luminance. Invest Ophthalmol Vis Sci. 1997; 38:207–218. [PubMed: 9008645]

30. Rabin J. Quantification of color vision with cone contrast sensitivity. Visual neuroscience. 2004; 21:483–485. [PubMed: 15518234]

31. Anastasakis A, et al. Clinical value, normative retinal sensitivity values, and intrasession repeatability using a combined spectral domain optical coherence tomography/scanning laser ophthalmoscope microperimeter. Eye (London, England). 2011; 25:245–251.

32. Chen FK, et al. Test-retest variability of microperimetry using the Nidek MP1 in patients with macular disease. Invest Ophthalmol Vis Sci. 2009; 50:3464–3472. [PubMed: 19324853]

33. Feigl B, et al. Cone-mediated multifocal electroretinogram in early age-related maculopathy and its relationships with subjective macular function tests. Current eye research. 2004; 29:327–336. [PubMed: 15590480]

34. Loshin DS, White J. Contrast sensitivity. The visual rehabilitation of the patient with macular degeneration. Archives of ophthalmology (Chicago, Ill : 1960). 1984; 102:1303–1306.

35. Puell MC, et al. Impaired mesopic visual acuity in eyes with early age-related macular degeneration. Invest Ophthalmol Vis Sci. 2012; 53:7310–7314. [PubMed: 23033386]

36. Dimitrov PN, et al. Visual function tests as potential biomarkers in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011; 52:9457–9469. [PubMed: 22003115]

37. Sunness JS, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. Ophthalmology. 1999; 106:1768–1779. [PubMed: 10485549]

38. Klein R, et al. The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. American journal of ophthalmology. 2008; 146:692–699. [PubMed: 18672224]

39. Lindblad AS, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. Archives of ophthalmology (Chicago, Ill : 1960). 2009; 127:1168–1174.

40. Jackson GR, et al. Twelve-month natural history of dark adaptation in patients with AMD. Optometry and vision science : official publication of the American Academy of Optometry. 2014; 91:925–931. [PubMed: 24705482]

Summary Statement

A prospective exploratory pilot study examined the test-retest reliability and feasibility of computerized alternative visual function studies in patients with dry age-related macular degeneration to improve early outcome metrics used to track and treat this disease. These included low luminance visual acuity, cone-specific contrast, contrast sensitivity, and microperimetry.
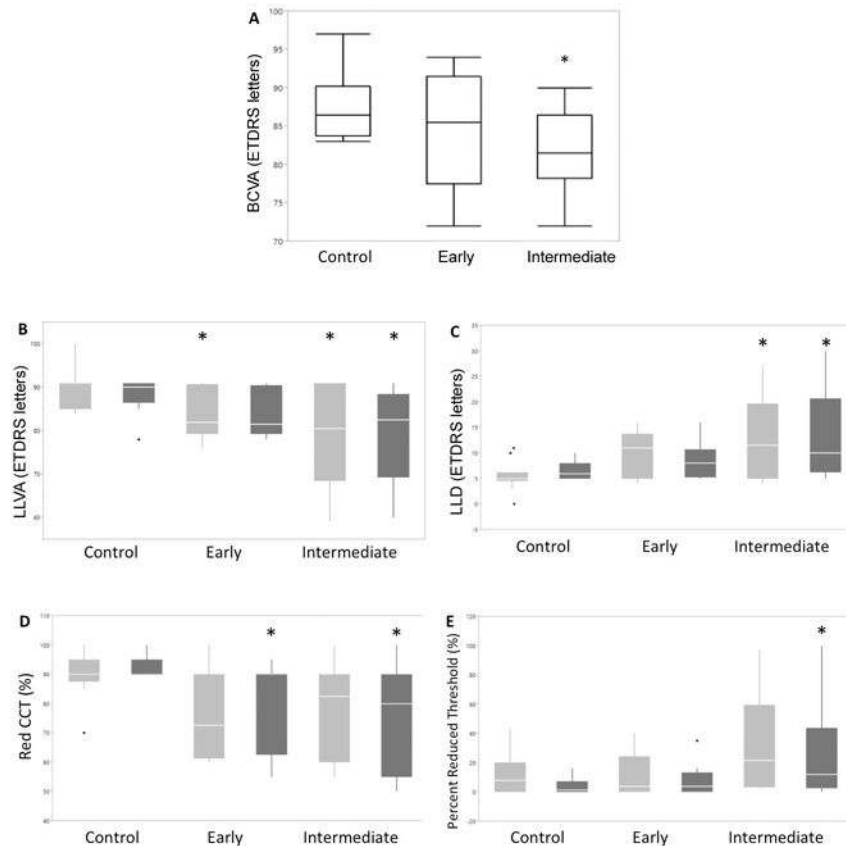
Figure 1.

Boxplots showing (A) best-corrected visual acuity (BCVA), (B) low-luminance visual acuity (LLVA), (C) low-luminance deficit (LLD), (D) Red Cone Contrast Test (CCT), and (E) Percent Reduced Threshold on microperimetry testing for control and each age-related macular degeneration (AMD) AREDS clinical group.

Each boxplot demonstrates outliers along with the maximum, upper quartile, median, lower quartile, and minimum values. (A) displays values collected during visit 1 only, while (B)-(E) show values from visits 1 and 2 in light and dark gray respectively. Black dots represent outliers while one asterisk denotes significance at the P <0.05 level when compared with controls at the same visit.

Groups did not vary with respect to baseline BCVA (A), however LLVA (B) and LLD (C) showed significant differences between control and intermediate populations. **D.** Both early and intermediate groups had differing performance compared to controls on the Red CCT test during the second visit. **E.** The intermediate AMD group was characterized by a significantly higher percent reduced threshold as compared to the control group. BCVA and LLD are reported as aggregate letters; Percent Reduced Threshold and Red CCT are both measured as percent.
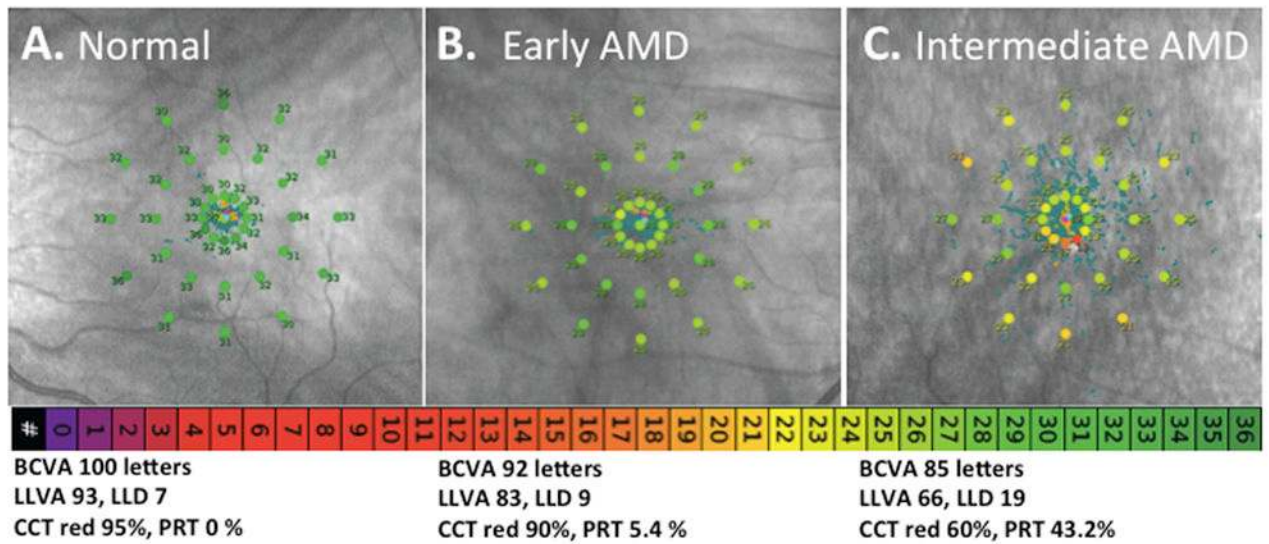
Figure 2.
A-C Retinal sensitivity on microperimetry testing of participants from each of the three groups (control, early AMD and intermediate AMD). Color scale bar on the bottom of the image represents retinal sensitivity value range for microperimetry. Note the difference in retinal sensitivity between the 3 subjects with increasing AMD pathology. The corresponding values for BCVA, LLVA, LLD (all expressed in ETDRS letters), CCT red (%), and PRT are shown for each subject.
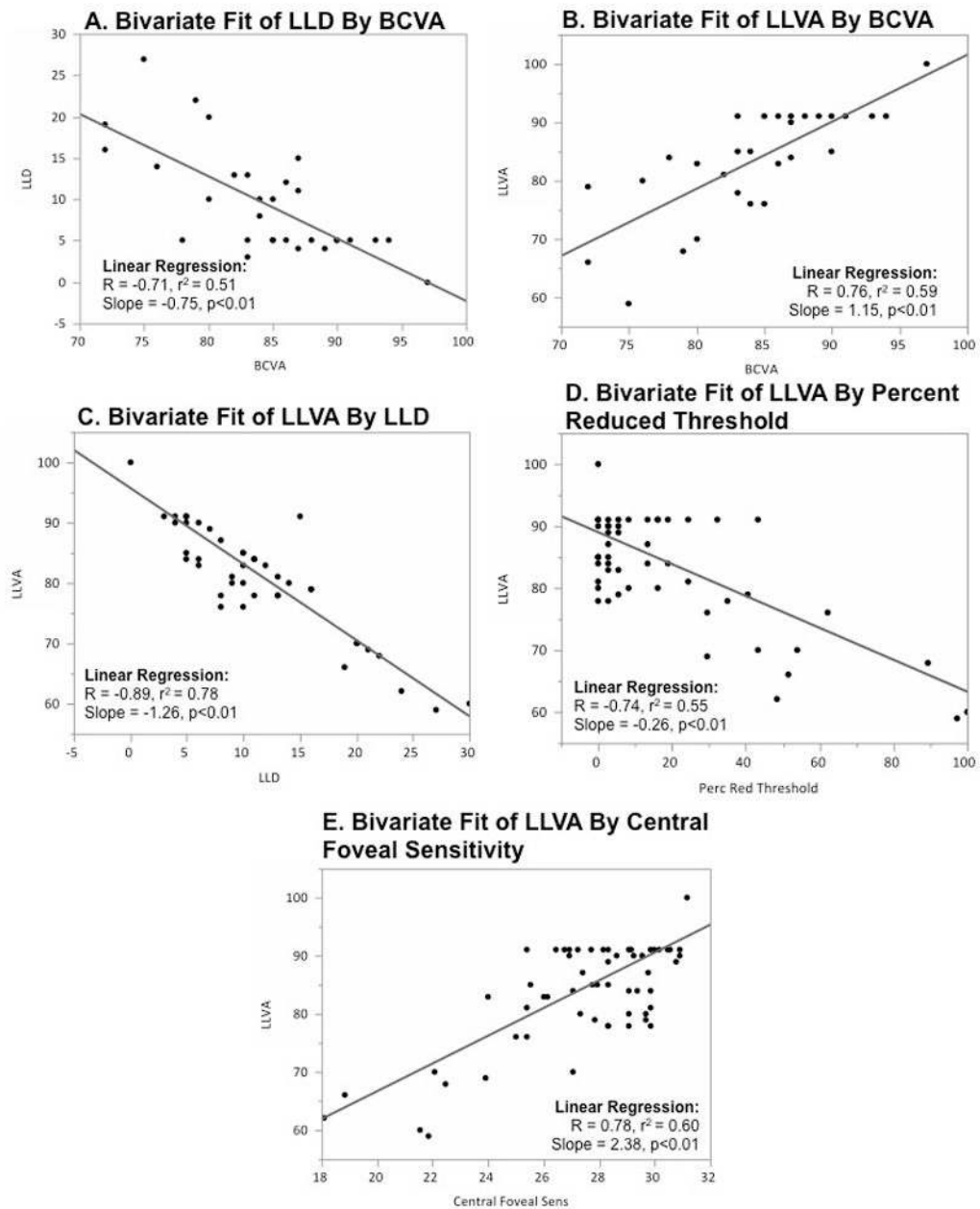
Figure 3.

Scatterplots examining the relationship between functional measures amongst all subjects. **A, B** show correlations indicating worse BCVA is associated with worse low light visual function. **C, D, E** demonstrate strong relationships between LLVA and LLD (reported in letters) and MAIA measures PRT (%) and central foveal sensitivity (dB).

Table 1

Subject demographics and group designation

Group	Control	Early AMD	Intermediate AMD	P value
Number of subjects	10	8	12	
Mean age (std dev)	69.2 (8.59)	67.5 (7.58)	71.83 (6.77)	0.45
Gender (% male)	60	62.5	58.3	1.00
BCVA range Snellen (ETDRS letters)	20/13 (97)-20/25 (83)	20/13 (94)-20/40 (72)	20/16 (90)-20/40 (72)	0.112
Cataract status				
Phakic N (%)	9 (90%)	7 (87.5%)	8 (66.7%)	0.45
Clear	1	1	0	
Trace NS	1	1	0	
1+ NS	2	4	5	
s ≥2+ NS	5	1	3	
Pseudophakic	1	1	4	

Table 2

Intrasession test-retest variability as described by intraclass correlation analysis and coefficient of repeatability for all subjects (A), control group (B), early AMD group (C) and intermediate AMD group (D).

A. All subjects

Variable	N	Intraclass Correlation	Lower Confidence Limit	Upper Confidence Limit	Coefficient of Repeatability
LLVA	30	0.86	0.73	0.93	9.34
LLD	30	0.87	0.76	0.94	6.27
Log contrast sensitivity	30	0.60	0.27	0.76	0.28
CCT Red	28	0.83	0.67	0.92	17.36
CCT Blue	28	0.79	0.60	0.90	15.37
CCT Green	28	0.75	0.53	0.87	20.94
Percent reduced threshold	30	0.83	0.68	0.92	27.77
Average threshold	30	0.90	0.79	0.95	2.78
Central foveal sensitivity	30	0.73	0.51	0.86	4.27

B. Control group

Variable	N	Intraclass Correlation	Lower Confidence Limit	Upper Confidence Limit	Coefficient of Repeatability
LLVA	10	0.51	0.00	0.85	8.69
LLD	10	0.52	0.00	0.85	4.88
Log contrast sensitivity	10	0.00	0.00	0.56	0.28
CCT Red	9	0.18	0.00	0.70	15.99
CCT Blue	9	0.87	0.56	0.97	7.30
CCT Green	9	0.67	0.12	0.91	13.46
Percent reduced threshold	10	0.21	0.00	0.72	29.25
Average threshold	10	0.68	0.17	0.91	3.21
Central foveal sensitivity	10	0.32	0.00	0.77	4.44

C. Early AMD group

Variable	N	Intraclass Correlation	Lower Confidence Limit	Upper Confidence Limit	Coefficient of Repeatability
LLVA	8	0.96	0.84	0.99	3.10
LLD	8	0.71	0.12	0.93	6.35
Log contrast sensitivity	8	0.67	0.02	0.92	0.28
CCT Red	8	0.79	0.32	0.96	19.59

A. All subjects

Variable	N	Intraclass Correlation	Lower Confidence Limit	Upper Confidence Limit	Coefficient of Repeatability
CCT Blue	8	0.09	0.00	0.71	22.71
CCT Green	8	0.31	0.00	0.81	30.97
Percent reduced threshold	8	0.93	0.70	0.98	10.58
Average threshold	8	0.96	0.84	0.99	1.07
Central foveal sensitivity	8	0.86	0.50	0.97	1.75

D. Intermediate AMD group

Variable	N	Intraclass Correlation	Lower Confidence Limit	Upper Confidence Limit	Coefficient of Repeatability
LLVA	12	0.84	0.56	0.95	12.21
LLD	12	0.90	0.70	0.97	7.20
Log contrast sensitivity	12	0.71	0.10	0.87	0.28
CCT Red	11	0.88	0.64	0.96	16.70
CCT Blue	11	0.91	0.71	0.97	13.53
CCT Green	11	0.90	0.69	0.97	16.44
Percent reduced threshold	12	0.86	0.60	0.96	33.77
Average threshold	12	0.92	0.75	0.98	3.17
Central foveal sensitivity	12	0.76	0.37	0.92	5.20