Functional Impact of Perifoveal Geographic Atrophy in Patients with Dry AMD: A Systematic Review

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ABSTRACT

Conventional parameters such as best-corrected visual acuity (BCVA) often grossly underestimate the profound visual limitations experienced by patients with perifoveal geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD). Foveal preservation in these patients means that BCVA is often only moderately impaired, despite significant challenges often reported in undertaking day-to-day vision-requiring tasks. BCVA may lead to a misrepresentation of the extent of real-world visual dysfunction in this clinical population and yet, is widely used as the gold standard measure in assessing patient eligibility for disability entitlements and driving. This systematic review investigated the relationship between microperimetry thresholds and performance on tests of functional vision and visual function in patients with perifoveal GA.

A systematic search of the Embase, CINAHL, Medline, PubMed and Web of Science electronic databases was conducted to identify all relevant studies published between January 2002 and December 2017 in the English language and involving human participants. A search of the grey literature was also conducted. Ten relevant articles were found and a critical appraisal undertaken.

Only two of the 10 studies investigated functional deficits specifically in patients with perifoveal GA. The remaining eight studies were more broadly defined and failed to sub-classify participants according to GA location. Microperimetry was found to represent a valuable tool in quantifying visual deficits in these patients and was much more sensitive than conventional measures, including BCVA and low-luminance visual acuity. This review highlighted the importance of a multimodal approach to assessment to better capture the real-world visual dysfunction experienced by patients with perifoveal GA.

Keywords: geographic atrophy, perifoveal, visual function, functional vision, microperimetry

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe, irreversible visual impairment and blindness among individuals over the age of 65 in developed countries.[1] Of its two principal forms – wet (neovascular; exudative) AMD and dry (atrophic; non-exudative) AMD – the latter is more common and constitutes 90% of all diagnosed cases.[2] Dry AMD is characterised by a gradual and progressive atrophy of the photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris.[1] In contrast, neovascular AMD is characterised by choroidal neovascularisation and involves leakage of blood including serous fluid and other constituents, into the sub-retinal and/or intra-retinal space.[2]

Vision loss owing to neovascular AMD can be delayed by anti-vascular endothelial growth factor (VEGF) therapy. However, no treatment exists for dry AMD. Current management is concentrated on delaying progression to advanced disease by controlling for known, modifiable risk factors such as dietary and smoking habits, body mass index, blood pressure regulation and glycaemic control.[3-7] Supplementation of dietary zinc, vitamins C and E[8,9] is recommended together with lutein and zeaxanthin for those with reduced dietary green and coloured vegetable consumption.[9]

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Hallmark findings in the early stages of dry AMD include whitish-yellow drusenoid deposits which can manifest with or without pigmentary abnormalities of the RPE (either hyper- or hypo-pigmentation). Drusen are accumulations of extracellular, amorphous debris subjacent to the basement membrane of the RPE.[10,11] Whilst these clinical findings alone do not typically cause overt central vision loss in patients, substantial functional decline can ensue especially with advancing disease.

Small, multifocal atrophic areas form and initially are only visible on ocular coherence tomography.[12] These gradually enlarge and coalesce to form clinically obvious geographic atrophy (GA)[13,14] that are visible as depigmented areas with prominent choroidal vessels and are hypofluorescent on autofluorescence imaging.[15] The areas of GA result in decreased threshold sensitivity or scotomata in the corresponding parts of the visual field.[16] Importantly, the percept is not a black 'hole' or 'gap' in the patient's visual field, but rather, the missing content is 'filled-in' based on information from the surrounding intact visual field in a 'filling-in phenomenon'.[17,18] The adapted area is inferred or extrapolated from visual information acquired in adjacent, intact parts of the visual field.[19,20] Impaired facial recognition, compromised reading ability, nyctalopia and fluctuating vision are often experienced by the patient.[21,22]

In a proportion of patients with dry AMD, the GA develops paracentrally and the fovea is spared, at least initially.[13,14] These atrophic regions sometimes develop in a 'U'-shaped horseshoe pattern and gradually coalesce to form a perifoveal ring of atrophy with the centremost fovea being preserved. The retinal atrophy produces an annular area of blindness in the patient's visual field surrounding the central fixation locus, referred to as a 'donut scotoma' or 'ring scotoma', but central acuity is preserved. Eventually, the fovea also becomes atrophic and the visual acuity may decline to 6/60 or worse.[14]

One of the greatest challenges to date lies in quantifying the profound visual limitations experienced by patients with perifoveal GA. To appreciate this, a distinction must first be made between two equally important yet fundamentally different aspects of vision loss – visual function and functional vision. Visual function describes how well the eye and visual system work.[23] It relates not just to the workings of the eye but the entire cortical visual pathway. Under visual function, tests such as visual acuity, perimetry, contrast sensitivity and colour vision are considered. Functional vision, as distinct from visual function, relates to how well a patient can perform vision-related activities, such as reading text, pouring liquids, and orientation and mobility.[23] This differentiation is important as the two concepts are not inextricably linked.[24] Good visual function does not necessarily translate into good functional vision. For patients with perifoveal GA secondary to dry AMD, a failure to appreciate this important distinction often leads to a misunderstanding of the patient's condition by family, friends and practitioners alike.

Historically, the most commonly used measure of visual function in both clinical practice and ophthalmic research is best-corrected visual acuity (BCVA). BCVA is widely accepted as the gold standard measure of macular function. Clinical trials often assess BCVA to determine the efficacy of new therapeutic agents and treatments. Government and other regulatory authorities also recognise BCVA as the gold standard when assessing patient eligibility for concession entitlements and reimbursement programs.[25-27] However, in patients with perifoveal GA, BCVA is not an accurate representation of the true level of visual dysfunction as it fails to assess all nuances of human vision which is a complex phenomenon. Foveal preservation in these patients means that BCVA is often only moderately impaired, for example, in the order of 6/7.5 to 6/12. Despite this, these patients typically report profound difficulty with reading and recognising faces, over and above what would be predicted on the basis of their acuity alone. This is because a full word or face may not 'fit' in the small spared central area that is surrounded by the area of GA, with respect to the visual angle subtended and the retinal image size. In an attempt to acquire more visual information, the patient may scan their environment by moving their head or eyes. This strategy can aid visual processing but enhanced visual processing occurs at the expense of time. A BCVA of 6/12 or better does not give an indicator of the struggle one may have had in the process of achieving this level of acuity, inclusive of the time taken or increased scanning. The greatest difficulty is often experienced when the patient is required to localise kinetic objects or read a passage of text. Hence, when taken as a stand-alone measure, BCVA can lead to a gross overestimation of a patient's visual capabilities in the real world. To base clinical trial endpoints and eligibility criteria, for example 'legal blindness', exclusively on parameters of visual function reflects a misunderstanding of the important distinction between visual function and functional vision, and the pathogenesis of dry AMD.

In light of an aging population, the global prevalence of AMD is increasing. There is a critical need to define the functional impact of perifoveal GA in patients with dry AMD and to explore the use of other measures to gain a more accurate depiction of functional vision in this clinical population. One such test of increasing utilisation in ophthalmic practice is microperimetry.[28] Microperimetry is a psychophysical diagnostic technique correlating threshold sensitivity of individual points on the retina with ophthalmoscopic retinal appearance in real time.[29] Location of fixation sites at the fovea and macula enable accurate follow-up test-retest examination as stimuli are projected directly onto the retina and the same retinal point is monitored via eye-tracking.[30-32] During testing, stimuli are projected in random order to measure macular threshold sensitivity at pre-determined

retinal locations, typically over the central 10° of the retina.[33] Retinal locations are registered at baseline and the same locations are measured on repeat testing. Various microperimetry outputs are obtained, including average threshold sensitivity, fixation location and fixation stability. In the clinical setting, microperimetry is becoming increasingly popular as a means of detecting functional deficits arising from dry AMD.[28]

It is crucial to be able to accurately quantify the efficacy of new treatments and pharmacological agents, and to understand how these new-age therapies translate into functional real-world improvements, beyond patient performance in the examination chair. There is a need for ongoing and future clinical studies to use more sensitive and appropriate endpoints to monitor disease progression and evaluate potential treatment responses. Consequently, this systematic review aimed to investigate the relationship between microperimetry thresholds and performance on both functional vision and visual function testing in patients with GA secondary to dry AMD, specifically those with perifoveal atrophy. The significance and strength of any correlation may lend support for or against the clinical usefulness of microperimetry in assessing the degree of functional disability in this clinical population.

METHOD

A systematic search of the Embase, CINAHL, Medline, PubMed and Web of Science electronic databases was conducted to identify all relevant studies published between January 2002 and December 2017 that explored the functional impact of perifoveal GA in patients with dry AMD using microperimetry. The database search was restricted by date as the first fully automatic microperimeter (Nidek MP-1; Nidek Technologies, Padua, Italy) was developed in 2002. Only full-text articles published in the English language and involving human participants were eligible for inclusion. No search restrictions were placed on study type, although editorial articles and opinion pieces were removed during screening by the reviewers.

All searches included a combination of key words: 'macular degeneration or age-related macular degeneration or age related macular degeneration or dry age related macular degeneration or atrophic age related macular degeneration or AMD or geographic atrophy or atrophy* or atrophi* or macular disease or degenerative macular disease or degenerative maculopath* or foveal sparing or scotoma* or ring scotoma*' and 'microperimet* or visual function or functional vision or visual disability or macular function or patient reported outcome* or PROM*' (where * indicates truncation).

Titles and abstracts identified by the search were screened by the first author (JB) as well as a second, independent reviewer who otherwise had no involvement in this paper. Any articles that did not meet the eligibility criteria or that were deemed non-salient to the aims of this review were excluded. Duplicates were identified and removed. The full text of the article was retrieved for all relevant studies and read thoroughly, including when it was unclear whether the study met the inclusion criteria. The reference lists of included studies were reviewed to search for other relevant papers potentially missed in the database search.

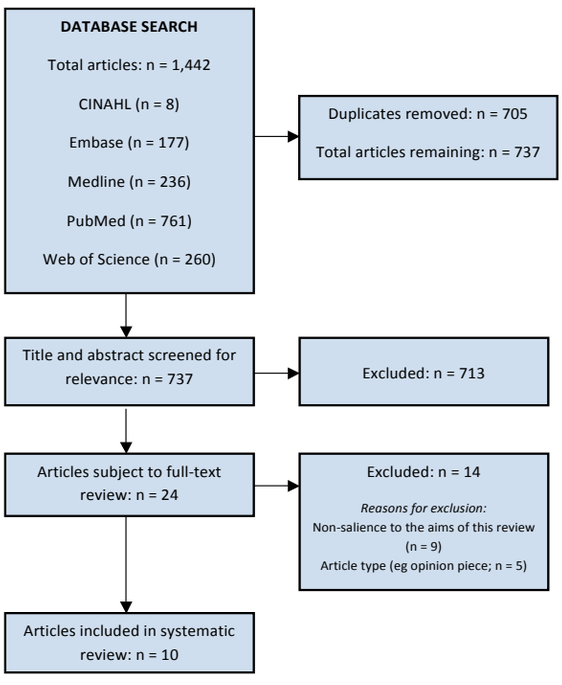

Figure 1. Flow-chart of article selection process.

A search of the grey literature was also conducted, including unpublished ophthalmology conference proceedings and theses in the field.

All included papers were critically evaluated using the Critical Appraisal Skills Programme (CASP) Research Checklist for Cohort Studies[34] or the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cross Sectional Studies[35] depending on study type. Each study was independently appraised by the two reviewers and the results cross-checked. In the event of a discrepancy, this was to be resolved by third party consultation with a senior investigator (WH).

RESULTS

The initial database search revealed 1,442 abstracts (Figure 1). A total of 705 duplicates were identified and removed. All remaining articles were screened for relevance. Once duplicates and papers that did not address the aims of this review were removed, 24 articles remained for potential inclusion. Of these, a further 14 were excluded upon full-text review owing to article type (opinion piece; n = 5) or non-pertinence to the topic (n = 9). Upon searching the reference lists and grey literature, no additional works relevant to the topic were found. A total of 10 articles were included in this systematic review. Table 1 describes these 10 studies, detailing the methodology and research findings. A critical appraisal using the CASP[34] and JBI Checklists[35] revealed these papers to be of moderate quality. The most common factors affecting study quality were: lack of a control or failure to include the control group in the data analyses, small sample size, single centre recruitment, or lack of longitudinal follow-up. There was complete agreement between the two independent reviewers for study quality. Heterogeneity across the studies with respect to the methodological approaches, sample characteristics and outcomes precluded a meta-analysis from being performed

Functional deficits measured using microperimetry in patients with perifoveal GA secondary to dry AMD

Only two of the 10 studies found in this review investigated functional deficits specifically in patients with perifoveal GA secondary to AMD.[36,37] The remaining eight studies were more broadly defined in terms of their sample and investigated patients with dry AMD, but did not further sub-classify participants according to the pattern of GA, that is foveal versus non-foveal involving.[38-45] As such, they did not conduct clinical subgroup analyses.

Of the two studies that specifically recruited participants with non-foveal GA secondary to AMD, both reported a significant reduction in mean retinal sensitivity outputs measured using the MAIA microperimeter in patients with AMD compared to healthy controls.[36,37] Moreover, they found that microperimetry was much more sensitive than visual acuity measures, including BCVA and low-luminance visual acuity (LLVA), in detecting functional deficits in this clinical population. Longitudinal observation further revealed that microperimetry can detect subtle changes over a 12-month period even when no change is demonstrated on BCVA or LLVA testing.[37]

Wu, Ayton, Guymer and Luu[36] conducted a cross-sectional study of 179 eyes with a spectrum of dry AMD clinical severity (early, intermediate, and non-foveal GA sub-groups; n = 101, 65 and 13 eyes, respectively) and 26 age-matched control eyes. They found that BCVA, LLVA and MAIA macular sensitivity were significantly reduced for all AMD groups when compared with controls, except for those with small drusen classified as between 63-125 μm and no pigmentary anomalies. Low luminance deficit, calculated as the difference between LLVA and BCVA, was significantly different from controls only in the non-foveal GA group but not in any other AMD group. Macular sensitivity was found to be significantly correlated with LLVA, but not BCVA. A significant, strong positive correlation between macular sensitivity and low luminance deficit was reported, suggesting that LLVA may detect a greater extent of functional deficit than BCVA in eyes with increasingly poorer retinal sensitivity. Using linear regression models for macular sensitivity and BCVA, and macular sensitivity and LLVA, it was estimated by Wu et al[36] that when a reduction of two standard deviations (SDs) away from normal for BCVA and LLVA was measured, a much greater decline in macular sensitivity of 6.1 and 3.7 SDs, respectively, was apparent. Hence, their findings suggest that microperimetry is a much more sensitive measure than BCVA and LLVA in detecting functional deficits in dry AMD. However, a notable limitation of this study was that it lacked any longitudinal follow-up with the majority of participants having been assessed at a single visit only.

Wu, Ayton, Luu and Guymer[37] investigated longitudinal changes in microperimetry and LLVA over a 12-month period in patients with dry AMD. Forty-nine eyes of 49 patients with dry AMD (n = 8 eyes with non-foveal GA, 41 eyes with intermediate AMD) and 10 eyes of 10 healthy controls underwent BCVA and LLVA testing, multimodal imaging, MAIA microperimetry and dilated fundus examination. Participants with AMD were assessed at three visits (baseline, 6 months and 12 months) and control participants seen at two visits (baseline and 12 months). Pathological progression was assessed in eyes with intermediate AMD by side-by-side comparison of coloured fundus photographs obtained at baseline and 12 months. Eyes were graded as 'stable', 'progressed/worsened', or 'improved'. No significant changes from baseline were detected in mean BCVA, mean LLVA or low luminance deficit in any group over the 12-month period. In eyes with non-foveal GA, a significant reduction in mean microperimetric point-wise sensitivity was detected at both 6 months and 12 months compared with baseline.

Table 1. Summary of the methodological approaches and outcomes of studies included in the systematic review

Study authors	Title of article	Study design	Primary aim/s	Methodology	Sample demographics	Key findings
Chandramohan et al (2016)[38]	Visual function measures in early and intermediate age-related macular degeneration	Prospective, controlled exploratory pilot study Single centre (Duke Eye Centre, Durham, USA)	To evaluate the test-retest repeatability of computerised tests of LLVA, cone-specific contrast (CSCT), contrast sensitivity, and MAIA microperimetry in dry AMD.	Participants underwent BCVA, LLVA, contrast sensitivity, cone-specific contrast testing, and MAIA microperimetry assessment at baseline and at follow-up examination conducted one-month later (± 10 days).	**n = 30 eyes of 30 participants (20 AMD patients and 10 healthy controls)** *8 with early AMD (AREDS Stage 2)*: Mean age 67.5 ± 7.6 years; 5 males, 3 females; Snellen BCVA range (ETDRS letters): 20/13 (94) – 20/40 (72) *12 with intermediate AMD (AREDS Stage 3)*: Mean age 71.8 ± 6.8 years; 7 males, 5 females; Snellen BCVA range (ETDRS letters): 20/16 (90) – 20/40 (72) *10 healthy controls*: Mean age 69.2 ± 8.6 years; 6 males, 4 females; Snellen BCVA range (ETDRS letters): 20/13 (97) – 20/25 (83)	High test-retest repeatability was found at one month for all visual function metrics (LLVA, CSCT and MAIA microperimetry; intraclass correlations >0.7) with the exception of log contrast sensitivity (intraclass correlations 0.6). Compared with age-matched controls, patients with intermediate AMD showed significant deficits on BCVA, LLVA, percent-reduced threshold on microperimetry and red CSCT but not on contrast sensitivity, green and blue CSCT.
Chen et al (2011)[39]	Nidek MP-1 is able to detect subtle decline in function in inherited and age-related atrophic macular disease with stable visual acuity	Retrospective exploratory review Single centre (Moorfields Eye Hospital, London, UK) No control	To investigate whether the Nidek MP-1 microperimeter can detect subtle functional decline in patients with progressive atrophic macular disease but stable VA.	Retrospective review of patient data collected at three routine clinical visits. Each patient had undergone three serial microperimetry tests at baseline, 6 months and 12 months. BCVA and fundus autofluorescence images were also performed at each visit. Changes in the following outcome measures were analysed for each of the three time-points: BCVA, fixation characteristics on microperimetry, retinal sensitivity on microperimetry (both *overall* mean macular sensitivity and *regional* sensitivity based on specific topographical and functional areas), and fundus appearance on autofluorescence imaging.	**n = 9 eyes of 9 patients with atrophic macular disease** Median age 59 years (range 38 – 76 years) Median LogMAR BCVA at baseline 0.3 (range 0.18 – 0.78) *3 with ABCA4 retinopathy (macular dystrophy)*: Median age 45 years (range 38 – 55 years); 1 male, 2 females *3 with GA secondary to AMD*: Median age 73 years (range 60 – 76 years); 1 male, 2 females *3 with macular dystrophy of unknown genetic cause*: Median age 59 years (range 41 – 68 years); 2 males, 1 female	Nidek MP-1 microperimetry can detect significant *regional* sensitivity decline in patients with atrophic macular disease, stable VA, and progressive atrophy on fundus autofluorescence. In particular, sensitivity within the central macular region and at the edge of a dense scotoma showed statistically significant decline within 6 months or 12 months. No significant change in overall mean macular sensitivity was observed over 12 months and no patient had a decline or improvement in overall mean MS beyond that which would be typical of test-retest variability (2.2 dB).
Dinc, Yenerel, Gorgun & Oncel (2008)[40]	Assessment of macular function by microperimetry in intermediate age-related macular degeneration	Retrospective review Single centre (Yeditepe University Eye Hospital, Istanbul, Turkey) Controlled	To evaluate retrospectively the central retinal function of patients with intermediate AMD using the MP-1 microperimeter.	Macular function was evaluated in all participants using the MP-1 microperimeter. Mean sensitivity (MS), mean defect (MD) parameters, fixation patterns, and fixation localisations were assessed. Testing was conducted during a single visit.	**n = 60 eyes of 60 participants (30 AMD patients and 30 healthy controls)** *30 eyes of 30 patients with intermediate AMD*: Mean age 67.7 ± 7.3 years (range 55 – 81 years); 16 males, 14 females; Mean Snellen BCVA between 20/32 – 20/20 *30 healthy eyes of 30 participants*: Mean age 68.7 ± 5.4 years (range 59 – 83 years); Gender breakdown not specified; Mean Snellen BCVA between 20/25 – 20/20	When microperimetry findings of patients with intermediate AMD were compared to the control group, mean macular sensitivity was significantly decreased and mean deficit significantly increased in the intermediate AMD group. Fixation was predominantly central and stable in most participants, however a small number of patients in the intermediate AMD group demonstrated unstable fixation and extrafoveal localisation.
Hartmann et al (2011)[41]	Scanning laser ophthalmoscope imaging stabilized microperimetry in dry age-related macular degeneration	Observational cross-sectional study Control group included but data from age-matched controls was not analysed Single centre (Jacobs Retina Centre, University of California, California) Testing conducted in a single visit. No longitudinal follow-up	To determine the effect of drusen and GA in dry AMD on focal retinal sensitivity using eye tracking SLO microperimetry, and to correlate retinal sensitivity with SD-OCT in these patients.	Retinal sensitivity was tested using the OPKO SLO microperimeter and structural fundus changes were measured with SD-OCT at precisely colocalised retinal points. Threshold perimetry was performed over individual drusen or retinal features. Drusen volume, diameter and height were graded, and inner segment/outer segment (IS/OS) junction integrity score calculated based on SD-OCT imaging.	**n = 44 eyes of 33 patients with drusen or GA secondary to dry AMD** *28 eyes of 22 patients with drusen secondary to dry AMD*: Age range 65 – 88 years; 8 males, 14 females; ETDRS BCVA better than 20/32 *16 eyes of 11 patients with GA secondary to dry AMD*: Age range 62 – 90 years; 7 males, 4 females; ETDRS BCVA ranged between 20/80 – 20/20 *25 age-matched control eyes from 16 patients*: Gender breakdown and age range not specified; ETDRS BCVA better than 20/32; Data from this group was not included in the analysis	SLO microperimetry can detect changes in retinal sensitivity in AMD patients overlying drusen and at the margin of GA. Retinal sensitivity overlying individual drusen was significantly reduced compared with the adjacent uninvolved retina. There was a significant correlation between retinal sensitivity and drusen volume, as well as IS/OS junction integrity. IS/OS junction integrity was found to be the strongest predictor of retinal sensitivity over other predictive factors such as drusen volume, diameter and height. In eyes with GA, an absolute scotoma was confirmed. Retinal sensitivity at the margin of GA was significantly decreased compared with the adjacent uninvolved tissue.
Meleth et al (2011)[42]	Changes in retinal sensitivity in geographic atrophy progression as measured by microperimetry	Prospective cohort study Single centre (National Eye Institute, National Institutes of Health, Bethesda, Maryland, US) Controlled	To characterise changes in macular sensitivity during GA progression over a 24-month period using microperimetry.	Retinal sensitivity of the central 20˚ of the macular was evaluated using MP-1 microperimetry every 6 months over a 24-month period. Microperimetric parameters of interest included number of scotomatous points, mean retinal sensitivity of responding points, and fixation stability. Autofluorescence imaging and coloured fundus photography was also obtained.	**n = 18 eyes of 9 patients with bilateral GA secondary to AMD** Patients had been enrolled in an interventional Phase II drug trial in which one eye had been randomised to treatment and the fellow eye observed (control) Mean age 76.8 ± 8.27 years (range 65 – 88 years) 3 males, 6 females Mean ETDRS BCVA at baseline 52 ± 17.6 letters (range 9 – 79 letters)	Mean number of scotomatous points increased significantly as a function of time (at a rate of 4.4 points per year). Mean retinal sensitivities of all tested points, all responding retinal points, and all peri-lesional points (responding points just outside of a functional scotoma) all decreased significantly with time, as did fixation stability. Growth of GA lesion area (based on fundus photography and autofluorescence imaging) was significantly associated with the observed changes in the number of scotomatous points but not with the changes in the other microperimetric parameters.

Midena et al (2007)[43]	Microperimetry and fundus autofluorescence in patients with early age-related macular degeneration	Cross-sectional study Single centre (Medical Retina Clinic, Department of Ophthalmology, University of Padova) No control Testing conducted in a single visit. No longitudinal follow-up	To compare microperimetry and fundus autofluorescence of the macular in patients with drusen and pigment abnormalities secondary to early AMD.	Retinal sensitivity was assessed on all participants using the MP-1 microperimeter. Coloured fundus photography and autofluorescence imaging of the macular were recorded at the same visit. Microperimetry results were topographically superimposed over FAF images.	**n = 13 eyes of 13 patients with bilateral early AMD** All eyes had presence of drusen and associated RPE changes, but no clinical evidence of GA Mean age 76.2 ± 6.55 years 3 males, 10 females ETDRS BCVA 20/20 in all eyes	A significant reduction in retinal sensitivity was observed over areas characterised by large soft drusen and/or pigment abnormalities. Large drusen had a greater impact on retinal sensitivity than RPE pigment abnormalities alone. However, when both characteristics were present the reduction was greater than compared with either characteristic in isolation.
Wu, Ayton, Guymer a&nd Luu (2014)[44]	Comparison between multifocal electroretinography and microperimetry in age-related macular degeneration	Cross-sectional study Multi-centre (private ophthalmology clinics and RVEEH, Melbourne, Australia) Controlled	To correlate and compare the magnitude of functional deficits obtained with mfERG testing versus MAIA microperimetry in eyes with intermediate AMD.	mfERG and MAIA microperimetry testing was performed on one eye of each participant. Thirteen hexagons in the central three rings of a 103-hexagon stimulus grid for mfERG and retinotopically matched points on microperimetry were chosen and converted into standard deviations away from that of control eyes (Z score) to represent the magnitude of measured functional deficit and allow a direct comparison of the two measures.	**n = 104 eyes from 104 participants** *60 eyes of 60 patients with intermediate AMD* Mean age 69.6 ± 7.5 years (range 51 – 89 years) Mean logMAR BCVA 0.02 ± 0.10 *44 eyes of 44 control participants* Age range 53 – 86 years Mean logMAR BCVA -0.13 ± 0.10	No significant correlation was found between average Z scores of retinal sensitivity with the average Z scores of mfERG implicit time or response amplitudes. Functional deficit measured using MAIA microperimetry was greater than that measured using mfERG (response amplitude and implicit time) for corresponding points at all three rings in eyes with intermediate AMD.
Wu, Ayton, Guymer & Luu (2014)[36]	Low-luminance visual acuity and microperimetry in age-related macular degeneration	Cross-sectional study Multi-centre (private ophthalmology clinics & RVEEH, Melbourne, Australia) Controlled	To compare the effectiveness of LLVA and microperimetry in assessing functional deficit in patients with dry AMD.	ETDRS BCVA, LLVA and MAIA microperimetry was performed on one eye of each participant. Low luminance deficit (LLD) was calculated as the difference between LLVA and BCVA. The results of functional testing were compared across 6 clinical severity groups. The relationship and strength of any correlation between different functional parameters was evaluated and compared.	**n = 205 eyes of 205 participants** *179 eyes of 179 patients with a clinical spectrum of different dry AMD severity (early, intermediate, and non-foveal GA)* Mean age and BCVA dependent on clinical severity classification – refer Table 1 (p. 1614) and Figure 1A (p. 1615) Gender breakdown not specified *26 eyes of 26 control participants* Mean age 65.5 ± 5.0 years BCVA data – see box plot data Figure 1A (p. 1615) Gender breakdown not specified	BCVA, LLVA and macular sensitivity were significantly reduced for all AMD clinical severity groups when compared with controls, except for those (in Group 2) with drusen between 63 and 125 µm. LLD in AMD clinical severity groups was not significantly different from control participants, with the exception of those in the non-foveal GA group. A significant positive relationship (R = 0.613) between macular sensitivity and LLD, but not BCVA, was found, suggesting that LLVA may detect a greater extent of functional deficit than BCVA in eyes with increasingly poorer retinal sensitivity.
Wu, Ayton, Luu & Guymer (2015)[37]	Longitudinal changes in microperimetry and low luminance visual acuity in age-related macular degeneration	Prospective, longitudinal study Single centre (Centre for Eye Research Australia, Melbourne, Australia) Controlled	To investigate whether microperimetry and LLVA can detect functional changes over a 12-month period in patients with intermediate AMD.	Participants underwent ETDRS BCVA, LLVA, multimodal imaging (CFP, NIR, SAF, SD-OCT), MAIA microperimetry (mean point-wise sensitivity [PWS]) and clinical examination. Participants with AMD were seen at three visits during a 12-month period at 6-month intervals (baseline, 6 months and 12 months) and all control participants were seen at two visits (baseline and 12 months). Pathological progression was assessed in eyes with intermediate AMD by visual comparison of coloured fundus photographs obtained at baseline and 12 months. Eyes were graded as 'stable', 'progressed/worsened', or 'improved'.	**n = 49 eyes of 49 patients with AMD and 10 eyes of 10 healthy controls** 41 eyes with intermediate AMD Mean age 68.8 ± 9.2 years (range 50 – 87 years) Gender breakdown not specified Baseline BCVA not specified 8 eyes with non-foveal GA secondary to AMD Mean age 69.1 ± 6.8 years (range 58 – 79 years) Gender breakdown not specified Baseline BCVA not specified 10 healthy controls Mean age 66.0 ± 3.5 years (range 60 – 72 years) Gender breakdown not specified Baseline BCVA not specified	No significant changes in BCVA or LLVA were detected in any of the groups over the 12-month period. A significant reduction in mean microperimetric PWS was detected at 12 months compared with baseline in eyes with intermediate AMD graded as stable or worsened. A significant improvement in mean PWS was detected in eyes graded as improved. A significant reduction in mean PWS was identified in eyes with non-foveal GA at both 6 months and 12 months compared with baseline. No significant change in mean PWS was detected over a 12-month period in control eyes.
Wu, Guymer & Finger (2016)[45]	Low luminance deficit and night vision symptoms in intermediate age-related macular degeneration	Cross-sectional study Multi-centre (private ophthalmology clinics & RVEEH, Melbourne, Australia)	To investigate the relationship between self-reported night vision symptoms and visual function measures in bilateral intermediate AMD.	All participants underwent BCVA, LLVA and MAIA microperimetry at a single visit. The Night Vision Questionnaire (NVQ-10) was completed by all participants at the same visit and used to assess the degree	**n = 200 eyes of 100 patients with bilateral intermediate AMD** Mean age 69.8 ± 7.4 years (range 51 – 81 years) 26 males, 74 females	Responses on the NVQ-10 significantly correlated with LLD but not BCVA, LLVA or MAIA microperimetry retinal sensitivity. Participants with the highest degree of self-reported night vision
		No control		of self-reported night vision difficulties experienced by the patient. Low luminance deficit (LLD) was calculated as the difference between LLVA and BCVA.	Mean BCVA (logMAR) of better seeing eye -0.03 ± 0.09 (range -0.22 to 0.16)	problems had significantly worse LLD than those with the least difficulty.

In eyes with intermediate AMD graded as either stable or worsened, a significant reduction in mean point-wise sensitivity was not identified by the second visit (6 months) compared with baseline, but was detected by the third visit (12 months) compared with baseline. In AMD eyes graded as improved, a significant improvement in mean point-wise sensitivity was detected at 12 months, but not 6 months. No significant change in mean point-wise sensitivity was detected over a 12-month period in control eyes. These findings demonstrate that microperimetry is capable of detecting subtle functional changes over a 12-month period in eyes with dry AMD, even when visual acuity outcomes remain seemingly unchanged.[37]

Collectively, the above two studies indicate that microperimetry represents a valuable tool in quantifying visual deficits in patients with non-foveal GA secondary to dry AMD and should be considered as a means of assessing the efficacy of novel interventions in patients.[36,37] However, an important methodological limitation of both studies was that the number of eyes in each non-foveal GA sub-group was small (n = 13 and 8, respectively). Larger studies are required to increase the generalisability of these findings. Additionally, both studies only correlated patient performance on microperimetry with visual acuity parameters. They did not investigate the relationship between microperimetry and other functional measures, such as reading speed or patient-reported outcome measures (PROMS) such as self-reported visual function and quality of life questionnaires, in this clinical population.

Patient-centred outcome measures often involve the participant reporting the degree of difficulty that they experience across a variety of different domains such as near function, distance function and colour appreciation.[46] Multi-factorial assessment is necessary in these patients because although psychophysical tests such as BCVA, LLVA and contrast sensitivity can reveal specific visual function deficits, they do not capture the entire range of effects that a disease might incur.[46] Additional studies incorporating a multimodal approach are warranted to more fully assess visual impairment in these patients and explore the relationship between different clinical endpoints.

Functional deficits in patients with dry AMD more generally

The remaining eight studies included as part of this systematic review explored functional deficits in patients with dry AMD more broadly.[38-45] As mentioned, they failed to differentiate the sample demographic with respect to foveal versus perifoveal GA involvement. As such, it remains unclear as to whether each sample did in fact include patients in the population of interest to us. Notwithstanding, the findings of these eight studies have been discussed below in the broader context of dry AMD.

Visual acuity and microperimetry parameters

Compared with controls, patients with dry AMD demonstrate significant deficits on BCVA and LLVA,[38] and microperimetry outputs including mean macular sensitivity[40,42] and percent-reduced threshold.[38] A longitudinal cohort study of nine patients (18 eyes) with bilateral GA secondary to AMD showed that mean retinal sensitivities of all tested points, all responding retinal points, and all peri-lesional points (responding points just outside of a functional scotoma) all decreased significantly with time.[42] Others, however, have failed to detect any significant change in overall mean macular sensitivity.[39] Chen at al[39] found no significant change in overall mean macular sensitivity measured using microperimetry over a 12-month period in their sample of nine patients (9 eyes) with progressive, atrophic macular disease but stable BCVA. Instead, they reported a significant regional sensitivity decline upon dividing the retina into specific topographical and functional areas, whereby sensitivity within the central macular region and at the border of dense scotomata showed significant decline within 6 months and 12 months of baseline. Another study similarly reported regional-based sensitivity changes, whereby retinal sensitivity at the margin of GA was significantly decreased compared with adjacent, uninvolved tissue.[41]

Incongruity in the above findings may be owing to differences in the methodology across studies. The retrospective review by Chen et al[39] was conducted at a single centre and included only nine eyes in the analyses. As such, the sample may not have been representative of the population and did not provide sufficient power to reach statistically valid conclusions. The other studies had small but somewhat larger sample sizes of 18 to 30 eyes.[40,42] Furthermore, the type of microperimeter used by the investigators differed across studies, with some using the Nidek MP-1 microperimeter[39,40,42] and others using the MAIA microperimeter[38] or OPKO SLO microperimeter.[41] This may have in turn led to differences in the microperimetric outcomes measured.

Correlation between microperimetry and patient-reported outcome measures (PROMs)

Only one of the 10 papers in this systematic review included PROMs as a clinical endpoint.[45] No other study incorporated PROMs, nor correlated self-reported outcomes with other observed measures of visual function and functional vision. Wu, Guymer and Finger[45] examined the relationship between night vision symptoms measured using the 10-item Night Vision Questionnaire (NVQ-10) with BCVA, LLVA and microperimetry. In their cross-sectional study of 100 patients with bilateral intermediate dry AMD, they found low luminance deficit but not BVCA, LLVA or microperimetric retinal sensitivity (neither mean sensitivity nor central sensitivity) to be significantly associated with the

degree of self-reported night vision symptoms measured using the NVQ-10. Participants with the highest degree of self-reported night vision problems had significantly worse low luminance deficit than those with the least difficulty. These findings suggest that low luminance deficit may be a useful measure that can be readily implemented in clinical practice and may better capture the degree of night vision symptoms experienced by patients with intermediate AMD than the conventional measure of BCVA.[45]

The NVQ-10 implemented by Wu et al[45] uses a 10-item scale adopted from four items of the 25-item National Eye Institute Vision Functioning Questionnaire (NEI VFQ-25), and six items of a night vision symptom list. It is important to note that whilst the NVQ-10 has been used previously in other studies involving AMD participants,[47,48] it has not been formally validated. As such, its internal validity remains unknown. Also, in the study by Wu et al[45] it is not specified how the NVQ-10 was administered. If the questionnaire was interviewer-administered by study personnel who were also involved in the patients' care, it is possible that participant responses were at high risk of bias. The lack of a control group also prevents a comparison between the degree of self-reported night vision symptoms experienced by patients with AMD versus those of healthy, unaffected individuals. Future studies might also benefit from the inclusion of other visual function and functional vision parameters, such as contrast sensitivity and near visual acuity, to further explore the relationship between these measures and PROMs.

Correlation between microperimetry and multi-focal electroretinography (mfERG)

Multi-focal electroretinography (mfERG) is being increasingly utilised in the study of eyes with dry AMD,[49-52] but to date few studies have investigated the relationship between microperimetry and mfERG in quantifying visual deficits owing to dry AMD.[44] A controlled cross-sectional study by Wu, Ayton, Guymer and Luu[44] found that microperimetry might be better able to detect subtle differences in retinal function compared to mfERG in patients with intermediate dry AMD.

When considering retinotopically matched points, no significant correlation was found between the average z-scores of microperimetric retinal sensitivity and mfERG implicit time, nor response amplitudes. Furthermore, the magnitude of the measured functional deficit captured by microperimetry was significantly greater than that measured by mfERG parameters.[44] A comparison of the converted z-scores for mfERG and BCVA testing further revealed that there was no significant correlation between mfERG parameters and BCVA outcomes. The measured functional deficit in mfERG implicit time was not greater than BCVA, and the measured functional deficit of mfERG response amplitude was significantly less than BCVA.[44] At the outset, microperimetry appears a sensitive means of assessing visual dysfunction experienced by patients with dry AMD, but further studies are necessary to ascertain its usefulness in evaluating visual deficits in patients with perifoveal GA specifically.

The current review was limited in that the data were non-synthesisable and heterogeneity in the methodological approaches and outcomes precluded a meta-analysis from being performed. Furthermore, the search was restricted to English language articles only and as such, non-English papers were not included in this review.

CONCLUSION

This systematic review identifies a clear need for additional studies with a specific focus on the sub-population of dry AMD patients with perifoveal GA. Notwithstanding their limitations, the above studies provide a platform for further research in this field and point to the usefulness of employing a battery of tests when assessing functional deficits in patients with dry AMD, rather than one sole method of testing. For ongoing and future clinical studies of GA, a multimodal approach to assessment will facilitate greater understanding of the nature and progression of this disease and the real-life impact it has on patients, beyond performance in the examination chair. Indeed, existing models used to assess patient eligibility for disability support need to shift away from strictly unimodal or bimodal methods of testing, for example BCVA +/- standard automated perimetry. Adopting a multimodal approach to assessment is especially necessary in this clinical population given the unique pathogenesis of the disease. Doing so will allow a more comprehensive evaluation of visual function and functional vision that will ultimately better capture the very real and oppressing limitations often experienced by these patients. Seldom does a visual acuity of 6/12 or better provide a true account of a patient's visual dysfunction in the real world.

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