LEARNING DOMAINS

CLINICAL PRACTICE

COMMUNICATION

PROFESSIONAL GROUPS

Dispensing opticians — CPD PROVIDER — General Optical Council

Optometrists — CPD PROVIDER — General Optical Council

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CPD CODE: C-109798

Age-related macular degeneration

By Kishan Gadhia MCOptom

It is commonly known that age-related macular degeneration (AMD) is one of the leading causes of blindness in Western populations. Therefore, it is a widely-researched condition that is commonly encountered in primary care optometry.

AMD was the leading cause of certifiable vision loss in England and Wales in the year ending 2013[1]. A Royal National Institute of Blind People (RNIB) report from 2021 stated that AMD accounts for 23 per cent of all patients living with sight loss and is responsible for 48 per cent of those registered blind or partially sighted in the UK[2]. The National Institute for Health and Care Excellence (NICE) reported a significant increase in AMD hospital activity between the years 2005/06 and 2013/14 and, therefore, an increased strain on resources[3].

The statistics do make for astonishing reading, but research shows that AMD is here to stay and these numbers are only likely to increase. Meta-analysis of the prevalence and incidence of AMD in the EU calculated projections up to 2050 showing a 15 per cent increase in AMD numbers[4]. Global data meta-analysis showed the prevalence of AMD affecting 196 million patients in 2020, growing to 288 million patients in 2040[5]. The list of statistics and projections continues – but this only highlights the current and future burden posed by AMD both locally and globally.

AETIOLOGY

As well as being labelled the leading cause of severe irreversible visual impairment of adults in the developed world, AMD is defined by NICE as: *"a potentially progressive disorder of the macula that typically affects people aged over 50 years"*[6]. Changes can occur unilaterally or bilaterally, and AMD is typically diagnosed when these changes are visualised.

The exact causes of AMD are unknown as it is multifactorial; however, preceding visually identifiable changes there are pathophysiological changes that can be described by taking a deeper look at the macula region.

The earliest detectable changes in AMD occur between the macula retina and the choroid. The outer layers of the retina is where connective tissue, blood vessels, outer segments of rod and cone photoreceptors, retinal pigment epithelium (RPE) cells, Bruch's membrane (BM), and the choriocapillaris are found.

The choriocapillaris beneath the fovea is adapted to facilitate the local supply of oxygen and nutrients via diffusion, and it has been argued that the region is more susceptible to age-related changes in the long term. These changes include accumulation of insoluble material in BM and, therefore, reduced diffusion flow in the choriocapillaris. This, in turn, eventually impacts the oxygen and nutrient delivery to the RPE and outer neural retina[7].

It is also argued that AMD results from thickening of BM and reduced fluid movement and, therefore, accumulation of lipofuscin between the RPE and the choroid. Accumulation of lipofuscin in the RPE has been described as causing altered metabolism and degradation of photoreceptors leading to accumulation of deposits beneath the RPE – defined as drusen. Loss and shortening of the outer segments of photoreceptors has also been documented in AMD research[8].

SYMPTOMS AND EFFECTS

Symptoms of AMD include:

- Metamorphopsia
- Painless loss or blurring of central vision
- Black or grey central scotoma in vision
- Difficulty seeing finer detail
- Photopsia
- Difficulty adjusting to different light conditions
- Visual hallucinations in severe cases[9]

These effects have a compound impact on a patient's general wellbeing. As AMD affects the elderly population, it can cause them to feel less confident and independent and more solitary. It can cause significant emotional distress, reduced quality of life and lead to patients needing help with key daily activities[10]. It has also been argued that as the patient's quality of life is reduced by AMD, it can be a risk factor for depression[11]. Loss of vision has also been shown to increase the number of falls and, therefore, overall confidence patients will have[12].

CLASSIFICATION

AMD is typically referred to as dry or wet, where dry AMD embodies macular changes without the presence of fluid, and wet AMD shows changes with fluid at the macula. The NICE classification of AMD is divided into two primary sub-groups of early and late AMD.

Early AMD is related to drusen changes and is further divided into low, medium or high-risk progression groups. Low risk of progression is medium drusen (63 to 124 micrometres in diameter) or pigmentary abnormalities only. Medium risk of progression is large drusen (125 micrometres or more in diameter) or reticular drusen or medium drusen with pigmentary abnormalities.

High risk of progression is cases of large drusen with pigmentary abnormalities, or reticular drusen with pigmentary abnormalities, or vitelliform lesions without significant visual loss (best-corrected acuity better than 6/18), or atrophy smaller than 175 micrometres and not involving the fovea.

Late AMD is further divided into groups of intermediate, wet active, dry and wet inactive AMD. Intermediate AMD is where there is RPE degeneration and dysfunction (presence of degenerative AMD changes with subretinal or intraretinal fluid in the absence of neovascularisation) or serous pigment epithelial detachment (PED) without neovascularisation.

Wet active AMD is classic choroidal neovascularisation (CNV), occult (fibrovascular PED and serous PED with neovascularisation), mixed (predominantly or minimally classic CNV with occult CNV), retinal angiomatous proliferation (RAP) and polypoidal choroidal vasculopathy (PCV).

Late dry AMD is geographic atrophy (in the absence of neovascular AMD) or significant visual loss (6/18 or worse) associated with dense/confluent drusen or advanced pigmentary changes with or without atrophy or vitelliform lesion. Wet inactive AMD is fibrous scar or sub-foveal atrophy or fibrosis secondary to an RPE tear or atrophy (absence or thinning of RPE and/or retina) or cystic degeneration (persistent intraretinal fluid or tubulations unresponsive to treatment)[13]. This is a more detailed way of classifying AMD, which relies on differentiating macula changes to enable personalised treatment plans.

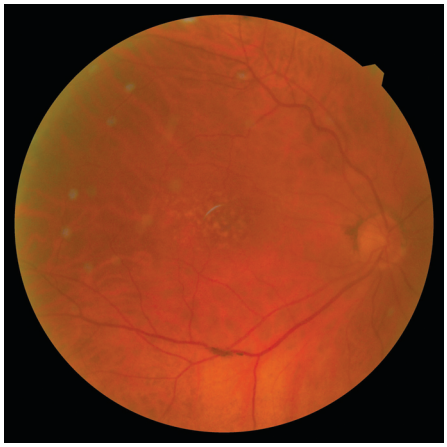

FIGURE 1: Dry AMD imaged via retinal photography

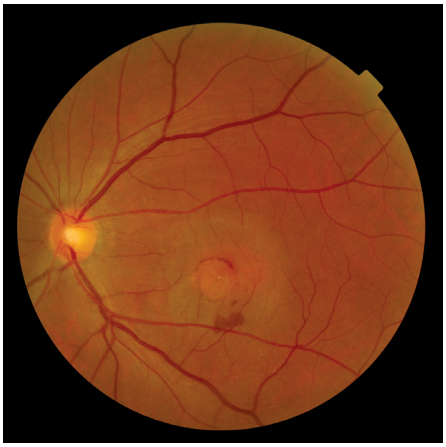

FIGURE 2: Wet AMD imaged via retinal photography

DIAGNOSIS

In both primary and secondary care, histology isn't readily available. AMD presentation is most commonly detected with retinal photography (RP), optical coherence tomography (OCT) scans and fundus fluorescein angiography (FFA). These techniques allow for effective detection, differential diagnosis, monitoring and screening for disease, especially in early and late AMD.

Both RP and OCT analysis are mainstays of current primary optometric care, with FFA most commonly used in secondary care. RP is the most superficial as it shows a 2D depiction of the inner retina with a camera, whereas OCT analysis allows depth imaging of the outer retina layers to the choroidal stroma using low-coherence interferomety[14].

RP and OCT are non-invasive whereas FFA is a more invasive procedure. It involves injecting sodium fluorescein intravenously, followed by a series of retinal photographs with blue (excitation) and green (barrier) filters to assess retinal vasculature and CNV activity[15].

In early AMD, drusen will be seen on retinal photographs as yellow circular shapes at – or around – the macula region. They can be isolated or multiple. Soft drusen are usually larger in size with indistinct margins. Conversely, hard drusen tend to be smaller with distinct margins.

Figure 1 and **Figure 2** provide examples of dry and wet AMD imaged via RP. OCT images would show nodular elevations of the RPE, which can be counted, measured and compared to previous images. FFA is rarely used in cases of early AMD. Drusen can be either hydrophilic or hydrophobic. Fluorescein is hydrophilic and, therefore, stains the hydrophilic drusen and appears as hyperfluorescent in the late stages of FFA[8].

In late AMD, retinal photographs can show the areas of geographic atrophy as well as blood accumulation at the macula. OCT imaging of geographic atrophy would show choroidal hyperreflectivity, absent external limiting membrane and BM and RPE changes. FFA would reveal geographic atrophy as a well-defined hyperfluorescent area with underlying choroidal fluorescence.

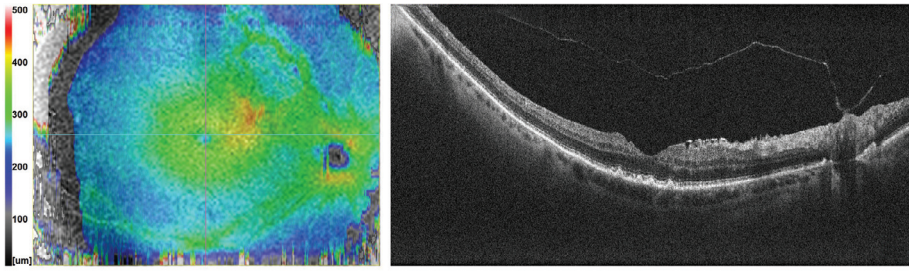

FIGURE 3: Dry AMD imaged via optical coherence tomography

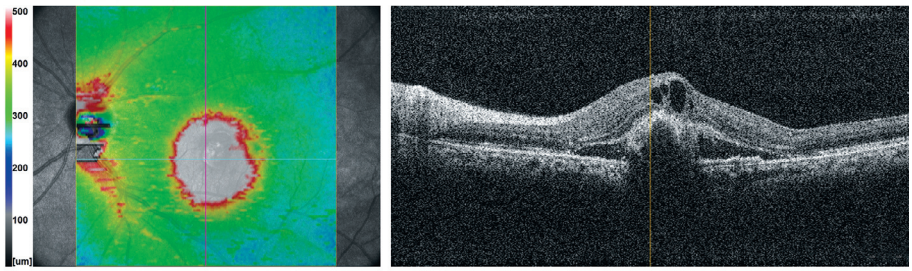

FIGURE 4: Wet AMD imaged via optical coherence tomography

In cases where wet active late AMD is present, OCT is particularly useful in determining the type of CNV by location and allows follow-up images to be compared to previous ones. **Figure 3** and **Figure 4** provide examples of dry and wet AMD imaged via OCT. Both OCT and FFA are used to determine the type of PED in wet active late AMD. Serous PED would show on OCT as dome-shaped hyper-reflective RPE over hyper-reflective BM, and as a well-defined lesion absent of leakage present until the late phase of FFA[8,14,15].

TREATMENT

There is no known treatment for early or late dry AMD, therefore, prevention and minimising progression is crucial. Vascular endothelial growth factor (VEGF) is an angiogenic growth factor that stimulates vascular permeability, therefore, anti-VEGF therapies are used as a first line treatment for late wet active AMD due to their anti-angiogenic properties[16,17]. Treatment is administered via intravitreal injection, typically monthly for three months, known as a loading phase, and then varied thereafter.

For treatment with anti-VEGF drugs to be commenced, certain criteria need to be met. These are that:

- Best corrected visual acuity is between 6/12 to 6/96
- There is no permanent structural damage to the fovea
- The size of the lesion is less than or equal to 12 disc sizes in greatest linear dimension
- There is evidence of presumed disease progression
- The manufacturer provides the drug with the discount agreed in the patient access scheme[16]

Ranibizumab is a monoclonal antibody against VEGF recommended by NICE for the treatment of wet AMD. Common systemic side-effects of Ranibizumab include anaemia, headache and nausea[18]. The TWEYEs study was carried out on 936 patients and showed low rates of adverse systemic side-effects[19]. Bevacizumab is an anti-VEGF treatment licenced for the management of carcinomas but does not have a UK marketing authorisation for use in the treatment of wet AMD and is, therefore, used off label[16,20].

The IVAN study was designed to compare the effectiveness of Ranibizumab and Bevacizumab when used to treat wet AMD. When visual acuity was measured at one year, the results were inconclusive. However, other measures such as foveal thickness and serious systemic adverse events were comparable[21]. Two years after the study, the visual acuities of the patients were measured again and showed that both Ranibizumab and Bevacizumab had similar results.

The key difference between the drugs is the cost, with two years of Ranibizumab treatment costing more than £18,500 and Bevacizumab costing £3,000[22]. This marked difference provides an immense opportunity to increase cost-effectiveness. Common side-effects of Bevacizumab include hypertension, vomiting and peripheral neuropathy[20].

Aflibercept has the highest affinity to VEGF out of all anti-VEGF drugs. Its systemic concentration after intravitreal administration is too low to cause systemic side-effects. However, pregnancy should be excluded before treatment[23].

The VIEW studies involved 2,419 patients and compared the efficacy of Aflibercept to treat wet AMD against Ranibizumab and concluded similar results across primary and secondary outcome measures[24].

Faricimab is a more recent anti-VEGF licenced for use to treat wet AMD by NICE[25,26]. The efficacy of Faricimab was compared to Ranibizumab in the AVENUE phase two randomised controlled trial over 36 weeks. Patients were divided into groups receiving different doses of Faricimab and Ranibizumab, and the results were measured via visual acuity and anatomical changes. It supported further phase three trials and showed no new or unexpected safety signals[27].

The STAIRWAY phase two randomised clinical trial lasted 52 weeks and compared the efficacy of quarterly dosing of Faricimab against monthly dosing of Ranibizumab. The results were measured by change in visual acuity from baseline at week 40, and the results were comparable with monthly Ranibizumab dosage[28].

Meta-analysis was carried out comparing Faricimab against other anti-VEGF agents in the treatment of wet AMD and diabetic macular oedema (DMO) by measuring the visual acuity and central subfoveal thicknesses of patients. No significant differences between Faricimab and other anti-VEGF drugs were found and supported more long-term studies to support the conclusions[29]. Another meta-analysis showed Faricimab achieving superior retinal drying and visual outcomes than Ranibizumab and Bevacizumab for patients with DMO[30].

A Cochrane Review of anti-VEGF therapy for wet AMD showed no significant differences in the safety and efficacy when comparing different anti-VEGF drugs[31]. As a result, it is crucial to treat the patient on an individual, patient-centred basis. For example, Ranibizumab may be the drug of choice for pregnant patients owing to its short half-life[32].

Due to the invasive nature of anti-VEGF treatment, ocular complications are possible. These include, but are not limited to, endophthalmitis, cataract and retinal tears or detachments. Although low, the risks of these should be minimised. Procedures that are in place include ventilation, decontamination, and single use equipment[33].

Prior to the development of anti-VEGF treatment, wet AMD was managed by destroying the neovascularisation. Laser photocoagulation would prevent further vision loss but create a scotoma[16,17]. Photodynamic therapy (PDT) with vertepeforin results in occlusion of the blood vessels and may be used as a second line treatment in combination with anti-VEGF drugs[16,17].

Meta-analysis compared combination therapy of PDT and Bevacizumab against Bevacizumab monotherapy. Five randomised controlled trials were included, with key measures of visual acuity and central retinal thickness. No significant differences of the indicators were found, and in the rates of ocular or systemic adverse events[34]. There was no significant difference when PDT was used in combination with either Bevacizumab or Ranibizumab.

However, combination therapy significantly reduced the number of injections required and thus the economic burden[35]. Furthermore, the injection process can be daunting to patients, therefore, fewer injections would be a positive for them. Medicine is continually evolving and the future of wet AMD treatment is exciting as research into gene therapy is currently underway.

RISK FACTORS

Risk factors for AMD are well researched and can be defined as modifiable or non-modifiable risk factors. The clue is in the name, as age is one of the main risk factors alongside family history of AMD and northern European ancestry[36]. Smoking is the main modifiable risk factor for development and progression of AMD and has been shown in studies to have toxic effects on the retina[37-40]. Although the risk increases with smoking amount and duration, cessation has been shown to reduce the risk of acquiring or progressing existing AMD.

Other modifiable risk factors are associated with poor general health including hypertension, cardiovascular disease, BMI of 30kg/m2 or higher and lack of exercise. These can all be drawn back to poor diet. Diets low in omega 3 and 6, vitamins A, C and E, carotenoids or minerals as well as too much saturated fat, high cholesterol and a poor glycaemic index can all contribute as risk factors of AMD[37].

AREDS REPORT NO.	INVESTIGATING	CONCLUSIONS
8	The effect of high-dose vitamins C and E, beta carotene and zinc supplements on AMD progression and visual acuity	The antioxidants and vitamins should be considered for patients older than 55 years with either early or late macula changes[42]
20	The association of lipid intake with baseline severity of AMD	Higher intake of omega 3 correlated with decreased likelihood of having neovascular AMD[43]
22	The relationship of dietary carotenoid and vitamins A, E and C intake with AMD	Higher dietary intake of lutein and zeaxanthin decreased the likelihood of having neovascular AMD, geographic atrophy and large or extensive intermediate drusen[44]
23	The relationship of dietary omega 3 with incident AMD	Higher intake of omega 3 reduced the risk of bilateral drusen progressing geographic atrophy[45]
35	Long-term effects of vitamins C and E, beta carotene and zinc supplements on AMD	Benefits for patients with neovascular AMD but not geographic atrophy

TABLE 1: AREDS report investigations and conclusions

Modifiable risk factors should be the focus of healthcare professionals through patient-centred care and advice and education. Recently, it has also been shown that one genetic locus – namely complement factor H – is an important gene in the pathogenesis of AMD.

REFLECTIVE SPECTROSCOPY

The LifeMeter is a device around the size of a biscuit tin that can be used to measure carotenoid levels in the skin as an indicator for a patient's ocular health and overall wellbeing. It uses a technique called reflective spectroscopy, which relies on sending light into the skin and measuring how much is reflected. The more light reflected signifies a higher level of carotenoids. The reading is taken from the index finger three times and the average of the results is the final 'score'.

With only 12 currently available in the world, the device is designed to be quick and easy to use in order to allow a large volume of patients to be screened within a single day. As optometrists' and dispensing opticians' scope of practice is continually evolving, the LifeMeter offers an additional mechanism by which to develop clinical practice and help patients in a novel way. In addition, the strong validity and repeatability of reflective spectroscopy, as well as its low cost and patient burden of measuring carotenoid levels in the skin, and its strong correlation to plasma carotenoid levels, has been reported[41].

Data from LifeMeter clinics show the average score is 250, and the results are used to classify patients into two primary groups. A score of 400 or more would place the client in the 'optimal' group, whereas a score of up to 400 would be classified as 'sub-optimal' and, therefore, would require further management to help improve the score. The sub-optimal patients would be invited to be screened again in six months to compare results to their baseline score.

SUPPLEMENTATION

Supplementation is a method of increasing carotenoid concentrations and, therefore, reducing the risk of developing or progressing AMD. It is a widely researched topic and the familiar Age Related Eye Disease Study (AREDS) reports were designed to evaluate the effect of carotenoid and vitamin supplementation for AMD progression.

Table 1 *(on the previous page)* provides details on the aims and conclusions of several of the AREDS reports relative to the content of this article. The AREDS supplement formulation was developed and contained vitamin C 500mg, vitamin E 400IU, 15mg beta carotene, 2mg copper and 80mg zinc. Importantly, report number 35 described the long-term (10-year) effects of AREDS formulation supplementation on AMD progression. The results showed benefits to those with neovascular disease but not central geographic atrophy[46].

AREDS 2 was a series of investigations to further study the effects of supplementation. AREDS 2 report number three assessed the substitution of beta carotene from the original AREDS formulation for lutein and zeaxanthin, as the former posed lung cancer risk to ex and current smokers. The conclusions suggested that lutein and zeaxanthin were more appropriate[47]. Report number 28 documented the long-term (10-year) effects of the switch and showed that lutein and zeaxanthin were less harmful as beta carotene nearly doubled lung cancer risk[48]. The AREDS 2 formulation was then finalised with beta carotene substituted for lutein 10mg and zeaxanthin 2mg, with other ingredients remaining unchanged.

Finally, report number 29 showed that following a Mediterranean diet of higher whole fruit, lower red meat and higher unsaturated to saturated fat ratio resulted in slower enlargement of geographic atrophy[49]. Diets like this are often hard to adhere to, especially for the elderly, hence supplementation is an effective and convenient way to ensure adequate intake of antioxidants and nutrients.

More recently, our knowledge of the macular carotenoids has been enhanced. It is known that lutein, zeaxanthin and meso-zeaxanthin accumulate at the macula where they are called macula pigments. Not only do macula pigments optimise normal vision but their role is also to protect against AMD by filtering blue light.

Research has shown that the distribution of the carotenoids in order from peripheral to central fovea is lutein, zeaxanthin and meso-zeaxanthin[50]. Meso-zeaxanthin was not part of the AREDS formulations as it was known to be produced by bioconversion of lutein. However, the exact quantities produced were unknown. Interestingly, studies showed that the addition of meso-zeaxanthin produced greater results in normalising macula pigment, especially centrally[51].

Investigation into the safety of supplementation with all three carotenoids demonstrated no adverse clinical complications[52]. The efficacy and safety of adding meso-zeaxanthin to the AREDS formula proves beneficial with the view of enhancing macula pigments and their role. There are many supplements available with varying degrees of ingredients; however, as healthcare professionals, it is our duty to make evidence-based recommendations to patients.

CONCLUSION

In conclusion, AMD is known to be the leading cause of vision loss and blindness, and its numbers are projected to increase. Not only does AMD cause irreversible ocular symptoms but it can also affect patients' wellbeing and quality of life. Classification of AMD helps to develop relevant treatment or monitoring plans for patients. Diagnostic techniques are advanced and can help us differentially diagnose and classify AMD accordingly.

Methods of treatment are only available for late wet active AMD and they are costly, a burden to patients and only prevent further loss of vision as opposed to reversing any changes. As a result, prevention of the disease becomes more paramount.

Risk factors can be modifiable or non-modifiable and the role of healthcare professionals embodies improving modifiable risk factors. Patient education and awareness should be made by evidence-based recommendations.

Directed reading is recommended into the NICE CKS AMD topic, the AREDS reports, and Professor John Nolan (profjohnnolan.com) who has carried out immense levels of detailed research into carotenoid supplementation.

REFERENCES

References can be found when completing this CPD module. For a PDF of this article with references email, abdocpd@abdo.org.uk

KISHAN GADHIA qualified as an optometrist in 2016, and has experience in both multiple and independent High Street practice – including in a practice specialising in dry eye disease diagnostics and management. He currently works for Bayfields Opticians and Audiologists, and his special interests include medical retina, myopia control, therapeutic prescribing and providing patient-centred care. An advocate for professional development, he is currently studying for the independent prescribing qualification, and has experience as a pre-registration supervisor.

LEARNING OUTCOMES FOR THIS CPD ARTICLE

DOMAIN: Communication

1.3: *Assist patients who may have or be at risk of developing age-related macular degeneration (AMD), in making informed decisions about their care.*

1.8: *Support patients in caring for themselves, including giving advice on the effects of life choices and lifestyle on their health and wellbeing in relation to the risk of developing or progressing with AMD, and supporting them in making lifestyle changes where appropriate.*

2.1: *Give patients information about risk factors for developing AMD, available methods of identifying risk and preventative considerations that are available, in a way they can understand. Use your professional judgement to adapt your language and communication approach as appropriate.*

DOMAIN: Clinical practice

5.3: *Be aware of current good practice in relation to the diagnosis and management of AMD, including modifiable risk factors, methods of identifying risk and preventative considerations, taking into account relevant developments in clinical research, and apply this to the care you provide.*

7.5: *Provide effective patient care and treatments to patients who may be at risk of developing or progressing with AMD, based on current good practice.*

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