Continuing Medical Education

The Diagnosis and Treatment of Age-Related Macular Degeneration

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Summary

Background: Age-related macular degeneration (AMD) is thought to cause approximately 9% of all cases of blindness worldwide. In Germany, half of all cases of blindness and high-grade visual impairment are due to AMD. In this review, the main risk factors, clinical manifestations, and treatments of this disease are presented.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed for original articles and reviews, as well as on current position statements by the relevant specialty societies.

Results: AMD is subdivided into early, intermediate, and late stages. The early stage is often asymptomatic; patients in the other two stages often have distorted vision or central visual field defects. The main risk factors are age, genetic predisposition, and nicotine consumption. The number of persons with early AMD in Germany rose from 5.7 million in 2002 to ca. 7 million in 2017. Late AMD is subdivided into the dry late form of the disease, for which there is no treatment at present, and the exudative late form, which can be treated with the intravitreal injection of VEGF inhibitors.

Conclusion: More research is needed on the dry late form of AMD in particular, which is currently untreatable. The treatment of the exudative late form with VEGF inhibitors is labor-intensive and requires a close collaboration of the patient, the ophthalmologist, and the primary care physician.

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Age-related macular degeneration (AMD) is the most common cause of irreversible vision loss in persons over age 65 in industrialized countries (1, 2). In 2020, some 200 million persons are affected by AMD worldwide. The disease accounts for approximately 9% of all cases of blindness (2). Even more importantly, the prevalence of AMD has risen markedly in recent years: in Germany, the number of persons with (mostly asymptomatic) early AMD rose from 5.7 million in 2002 to ca. 7 million in 2017—an increase of ca. 23% in 15 years (3–6). The later stages of AMD, which are often highly symptomatic and threaten to impair vision permanently, also became more common in Germany over the same period, from ca. 360 000 to ca. 490 000 persons—a rise of ca. 36% (6). It is estimated that half of all cases of blindness and high-grade visual impairment in Germany are due to late stage AMD (7, 8). In patients with a later stage of AMD, neovascular AMD is 1.4 times more common than geographical atrophy (the final stage of dry late AMD) (9). The rising prevalence figures may be due not only to the aging of the population, but also to better ascertainment through improved diagnosis. In any event, the strong effect of the demographic trend on the prevalence of AMD can be seen in the rise of the age-adjusted prevalence of the disease from 24% in persons aged 65 to 74 (3) to more than 44% in persons aged 70 to 95 (5).

The major effect of age on the emergence of AMD is also reflected in the fact that persons under age 50 generally display very few of the typical changes of AMD, or none at all. On the other hand, according to the Gutenberg Health Study carried out in Mainz, Germany, 24% of persons aged 65 to 74 already have typical changes of

Prevalence

The main risk factor for AMD is age. Its prevalence in industrialized countries is, therefore, steadily rising as the population ages.

Figures for Germany

Approximately 7 million persons in Germany now have AMD.

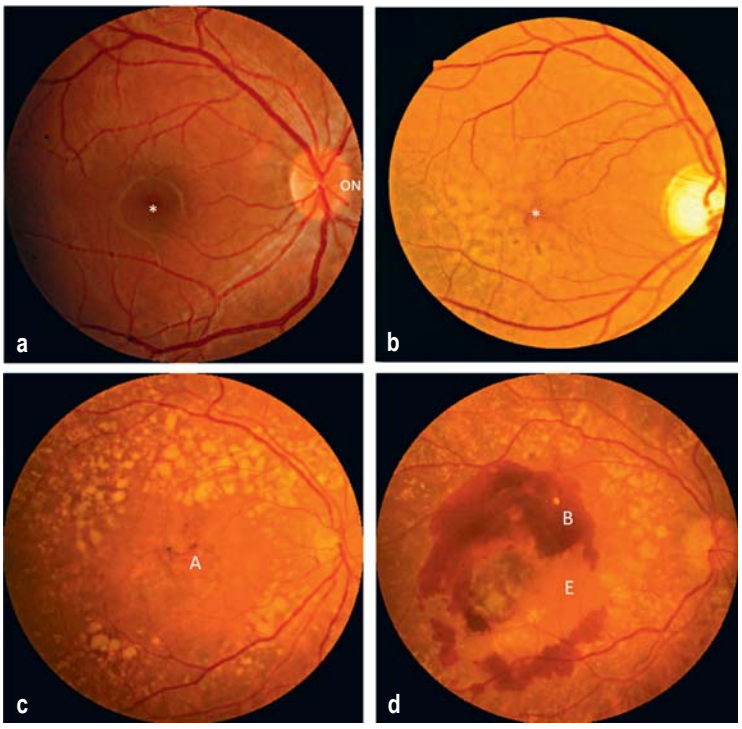

Figure 1: stages of age-dependent macular degeneration (AMD)

a) Normal juvenile macular image. The optic nerve (ON) is seen at right, as it enters the globe together with the retinal arteries and veins. The blood vessels form an arc around the macula, which is itself free of larger vessels. Around the center of the macula, i.e., the fovea (*), the physiological juvenile macular reflex can still be seen.

b) Early to intermediate AMD, with numerous, partly confluent drusen, mainly temporal to the fovea (*). Drusen are typically yellow deposits of non-degraded metabolic products under the retina.

c) Dry (atrophic) form of late AMD; many drusen are seen along the vascular arcades, and a punched-out area of atrophy (A) is seen in the center.

d) Wet form of late AMD (exudative or neovascular AMD); abnormal blood vessel growth in the choroidal plexus below the retina has led to exudation (E) and bleeding (B) into the macula.

AMD, although these are still asymptomatic in many cases (3). Most of the early AMD-related changes that were seen involved funduscopically visible deposition of metabolic products below or above the retinal pigment epithelium of the macula, i.e., so-called drusen and pseudodrusen (e1). The older the patient cohort under study, the more commonly such changes are found. The AugUR cohort study in Regensburg, Germany, for example, revealed intermediate-stage AMD in 44% of subjects aged 70 to 95, and late AMD in 19% of the same group (5). In other studies, the prevalence of AMD in persons over age 85 has been estimated at 30% (10).

Learning goals

This review will enable the reader to:

- know the prevalence and risk factors of AMD
- recognize its typical manifestations and know how to proceed with the diagnostic evaluation
- know how each stage of the disease is treated, and be acquainted with the complications of treatment.

Method

This review is based on pertinent publications retrieved by a selective search in PubMed for original articles and reviews, as well as on current position statements by the relevant specialist societies.

Progression of AMD

64.5% of patients with AMD have the same stage of the disease in the both eyes (11). In asymmetrically affected patients, the progression of the disease in the better-seeing eye is of paramount importance. Three large-scale population-based studies have shown that, if only a single eye is affected when the patient is initially diagnosed with AMD, the second eye becomes affected within 5 years in 19% to 28% of cases (12).

Late AMD is much more relevant to vision than early AMD, which is often asymptomatic, or intermediate AMD, which is usually oligosymptomatic *(Figure 1)*. The rate of progression from intermediate to late AMD in the natural course of the disease is usually given as 28% in five years (13). The initial symptoms often consist of distorted vision or visual loss in the center of the visual field. This is often described as immobile, centrally situated gray spots *(Figure 2)*. Late AMD comes in two main forms: the dry or atrophic form, and the wet or exudative (neovascular) form. Atrophic AMD is characterized by the slowly progressive loss of retinal pigment epithelium, photoreceptors, and choroidal capillaries in the macular region, which is the area of sharpest vision. It generally progresses slowly over several years and can lead, in advanced stages, to a complete loss of central vision, i.e., a central scotoma. Studies on the natural course of AMD have shown that, among eyes with intermediate AMD, atrophic areas arise in 19% within 5 years (14). Peripheral and orienting vision are preserved even in late AMD, because the degenerative process only affects the macular region, sparing the rest of the retina. As the macula is the central part of the retina with the highest spatial resolution, patients with AMD often have increasing difficulty reading and recognizing objects and faces; spatial orientation, however, is preserved through the intact functioning of peripheral vision *(Figure 2b)*.

Stages of AMD

AMD is subdivided into early, intermediate, and late stages. Late AMD, in turn, is subdivided into two types: dry (atrophic) and neovascular (wet, exudative) late AMD. A mixture of both types of late AMD is not uncommonly found in the same eye.

Functional impairment

The disease affects the macula and thus impairs vision in the center of the visual field, limiting the patient's ability to read, drive a car, or recognize faces.

The exudative form of late AMD is usually associated with much more rapidly progressive loss of vision than the atrophic form. Reading ability may be lost over the span of a few days. Untreated patients with exudative AMD lose an average of three lines (15 letters) of visual acuity in two years (15). The visual loss in the exudative form is explained by the development of choroidal neovascularization (CNV) in the macular area. The newly formed vessels can tear acutely, causing hemorrhage into the macula with secondary scarring. Pathological neovascularization probably reflects an attempt of the damaged retinal areas to repair themselves, which is complicated by exudation or tearing of the abnormal vessels and/or the retinal pigment epithelium, leading to rapid worsening of vision *(eFigure 1)*. The dry and exudative forms of AMD thus take very different courses despite their common beginning, with degeneration of the retinal pigment epithelium. Transitional or alternating forms between these two main forms are also encountered.

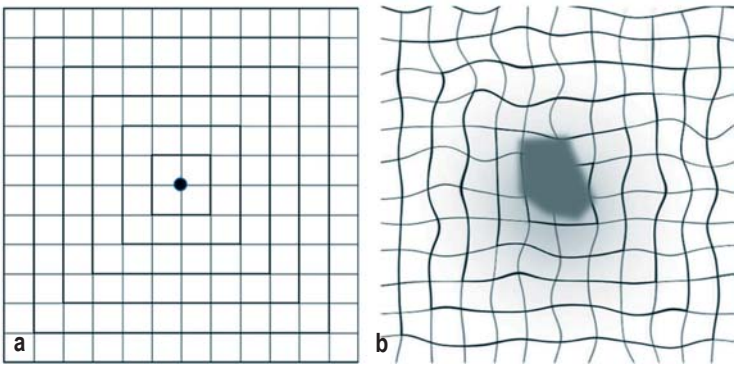

Figure 2: Clinical manifestations of age-dependent macular degeneration (AMD)
a) Amsler test with normal retinal findings: the lines are straight, and the fixation point is seen at the center.
b) Typical Amsler test findings in late AMD: the central fixation point cannot be seen because of a gray spot in the center of the visual field (central scotoma), and the lines appear distorted (metamorphopsia).

Risk factors of AMD

The main risk factor for AMD is age. As a pathogenetic hypothesis, it is thought that the very high metabolic activity of the macula places a high cumulative demand on the retinal pigment epithelium over the individual's lifetime for the breakdown and removal of metabolic waste products. AMD arises when the cells of the retinal pigment epithelium can no longer keep up with this demand in old age (e2). AMD, however, is not necessarily accompanied by other typical diseases of aging, such as osteoporosis (e3). Rather, there are other risk factors besides age that modulate both the emergence of AMD and its progression. The main modifiable risk factor is smoking: smokers have an odds ratio of 2.6 to 4.8 for the emergence of AMD, compared to non-smokers (16). Former smokers, too, have an elevated odds ratio of 1.7 for the emergence of AMD (16).

Aside from smoking, multiple genetic risk alleles for AMD have been identified in recent years. The two most important ones are polymorphisms in *CFH* (complement factor H) and *ARMS2* (age-related maculopathy susceptibility 2) (17–20). These two alleles together account for up to 45% of the risk of developing AMD (21). Moreover, a number of studies have revealed associations between AMD and the body-mass index, cardiovascular disease, and arterial hypertension (e4). Dyslipidemias and metabolic dysfunction have also been found to be associated with AMD in some studies, but putative causal relationships have not been clearly demonstrated (e5, 22). The drusen deposited in AMD resemble the atherosclerotic deposits in vascular walls that are typically seen in cardiovascular high-risk patients, but studies on a possible association between AMD and atherosclerosis have yielded conflicting results to date (e6).

Diagnostic evaluation of AMD

Patient history can reveal clues to the presence of AMD. Patients with AMD often report either acute or insidious worsening of vision in one or both eyes, which often becomes more apparent in dim light. The patient should be asked about distorted vision (metamorphopsia), which, if present, implies macular disease. The phenomenon of metamorphopsia can manifest itself when the patient looks, for example, at road stripes, windowpanes, or tiles in the kitchen or bathroom. Many patients also report that faces seem peculiarly disfigured, or that the images in the two eyes are of different sizes. Patients may be asymptomatic for a long time, however, if they are still in an early stage of the condition, or if the fovea is not (yet) involved. Thus, the proper diagnostic evaluation of AMD must always include an ophthalmological examination with measurement of best corrected visual acuity, funduscopic evaluation with dilated pupils, macular layer imaging with optical coherence tomography (OCT), and, sometimes, fluorescein angiography (at least in those cases where there is evidence of a possible need for treatment of exudative AMD) (23).

Exudative late AMD

The exudative type of late AMD shows the most aggressive course of all subtypes of the disease. It often causes rapid deterioration of central visual function through the pathological growth of blood vessels, along with exudation, bleeding, fibrosis, and sometimes tearing of the retinal pigment epithelium.

Genetic risk alleles

Aside from age, smoking and risk alleles in the genes of the complement system and the ARMS2 HTRA locus are the main risk factors for the emergence and progression of AMD.

OCT, in particular, now plays a key role in the diagnostic evaluation of AMD. (It was accordingly assigned an "EBM number," i.e., a reimbursable procedure code, by the National Association of Statutory Health Insurance Physicians in Germany in 2019.) OCT is noninvasive and can be performed with ease in nearly all patients. It must be emphasized that minimal standards of OCT image quality must be met so that small, but clinically relevant changes will not be missed (24). It must also be emphasized that neither OCT alone, nor the related technique of OCT angiography, can wholly replace classic fluorescein angiography for the differentiation of dry from exudative late AMD. Fluorescein angiography is the only technique that can directly reveal active exudation from pathologic blood vessels into the retinal parenchyma *(eFigure 2)*.

Treatment

The appropriate treatment for AMD depends on the stage of the disease. In all stages, the elimination of risk factors is clearly advisable; above all, smoking cessation. Multiple prospective population-based studies have shown that smokers have a higher risk of progression of AMD than non-smokers, even after AMD has been diagnosed (25). A Korean study further showed that the gain of visual acuity under anti-VEGF treatment is lower in smokers with exudative AMD than in non-smokers (26). Early detection of AMD may thus help motivate the patient to change lifestyle habits that promote the progression of the disease.

Dietary supplements for AMD are widely discussed in the literature. The most robust clinical trial data in this area are derived from the ARED trials (13, 27). AREDS-1 and AREDS-2 were randomized, controlled trials, each of which took several years to carry out, that investigated the putative effect of dietary supplements on the progression of AMD. The main finding of AREDS-1, published in 2001, was that high-dose supplementation with vitamin C and E, beta-carotene, and zinc had a positive effect in patients with intermediate-stage AMD (13). This must, however, be viewed together with findings from other studies, that found a higher rate of cancer in active or former smokers receiving high-dose supplementation of beta-carotene and vitamins. A combination of vitamin E and beta-carotene reportedly increased the risk of lung cancer by 18% (95% confidence interval [3; 36%], $p = 0.01$), while supplementation with vitamin and A and beta-carotene was associated with a relative risk of 1.28 ([95% CI 1.04; 1.57]; $p = 0.02$) (e7, e8). This led to a change in the dietary supplements used in the AREDS-2 trial, in which beta-carotene was replaced with lutein/zeaxanthin and omega-3 fatty acids (27). The efficacy of this type of dietary supplementation given in AREDS-2 was only shown for patients who were already in an intermediate or late stage of AMD, and the achieved effect sizes were considerably smaller than those achieved by smoking cessation. The odds ratio for AMD progression in AREDS-1 was 0.72 (99% CI [0.52; 0.98]) (13). The hazard ratio in the AREDS-2 trial was 0.89 (98.7% CI: [0.75; 1.06]) for supplementation with lutein + zeaxanthin + omega-3 fatty acids (docosahexaenoic acid [DHA] + eicosapentaenoic acid [EPA]) (27). Supplementation was found to have only a small effect on intermediate-stage AMD, and no effect was found in the early or late stages of the disease. Thus, no general recommendation can be given for the consumption of dietary supplements as preventive treatement (i.e. before signs of intermediate AMD are present) (e9). Rather, the German ophthalmological societies recommend a balanced diet for primary prophylaxis, in accordance with the recommendations of the German Nutrition Society *(Deutsche Gesellschaft für Ernährung)* (28, 29).

Another type of treatment that has been tried recently for intermediate-stage AMD, i.e., for the stage of the disease in which large drusen are already seen, but no atrophy or exudation is yet present (30), is nanosecond laser therapy of drusen. The LEAD trial addressed the question whether such laser treatment of drusen could slow the progression of AMD in patients with intermediate-stage AMD. The primary endpoint was not reached, i.e., no protective effect of laser treatment was found. In the subgroup of patients with so-called reticular pseudodrusen, the disease actually progressed faster (31). Thus, retinal laser therapy should not be performed in patients with dry AMD, except in the setting of a controlled clinical trial (32).

Dry (atrophic) late AMD

No effective treatment is yet available for the atrophic late form of AMD. All of the clinical trials carried out to date have yielded negative results, including recent ones that have focused on modulators of the complement system (33). The same reasons are generally cited for these failures as for the failure of treatment for other degenerative diseases of the central nervous system: in particular, that the treatment has presumably been initiated too late in the course of a disease cascade that has already reached a point of no return. At a certain stage in the disease process, neural tissue—in this case, the retinal

Symptoms that point to an AMD diagnosis

Clues to the diagnosis of AMD are provided by the typical symptoms, including distorted vision (metamorphopsia), loss of visual acuity, and central scotoma.

The main techniques of clinical evaluation

These include visual acuity testing, bilateral fundoscopy with dilated pupils, optical coherence tomography (OCT), and, in some cases, fluorescein angiography. Metamorphopsia can be recognized early by the patient with the aid of an Amsler grid.

photoreceptors—has been irreversibly lost; nor has any way yet been found to prevent the further loss of photoreceptors at the periphery of the already atrophic regions of the macula. Clinical research into the atrophic late form of AMD now centers on gaining a better understanding of the pathogenesis of disease progression, so that future interventions can be directed at the most promising targets and applied with optimal timing.

Wet (exudative) late AMD

At the beginning of this article, the aging of the population was cited as a likely reason for the increasing prevalence of AMD. As a logical consequence of this, one would expect to have seen a marked increase in the number of cases of blindness or severe visual impairment over the past few years; yet statistics from Germany (7) and other countries (34) reveal a stagnation, or even a decrease, in the rates of blindness and severe visual impairment, even though the prevalence of AMD has measurably risen. This is presumably largely due to the introduction, in 2005, of an effective treatment for the most aggressive form of AMD, the exudative late form (35). In 2006, after the publication of two successful phase 3 clinical trials, the journal Science listed anti-VEGF therapy for exudative macular degeneration as one of the top ten scientific breakthroughs of the year (e10). In this form of treatment, an anti-VEGF drug is injected directly in the vitreous body of the eye (intravitreal administration). Four such drugs are now available, one of them off-label (bevacizumab, in use since 2005) and three that have been approved for use in Europe: ranibizumab (approved 2007), aflibercept (approved 2012), and brolucizumab (approved 2020). The three approved drugs each cost approximately 1000 euros per injection, while bevacizumab costs only approximately 40 euros. Bevacizumab is not expected to be approved for intraocular use. Multiple other biosimilar drugs are likely to become available in the next few years.

Although the various anti-VEGF drugs differ from one another, sometimes markedly, in their chemical structure, binding affinity, and specificity, they share a common mechanism of action, i.e., the blocking of vascular endothelial growth factor (VEGF). VEGF is both a pro-angiogenic factor that promotes the formation and growth of pathological blood vessels in exudative AMD and a permeability factor that facilitates the extravasation of blood plasma components out of blood vessels into the retinal parenchyma. The deposition of sub- and/or intraretinal fluid from hyperpermeable choroidal vessels is one of the main causes of the worsening of vision associated with exudative AMD *(eFigures 1, 2)*. Much of the effect of VEGF inhibitors against wet macular degeneration comes from the reduction of vessel permeability, rather than from the inhibition of angiogenesis.

Unfortunately, anti-VEGF therapy must be given repeatedly over a long period of time in almost all patients, at least in the first few years of treatment (36). The patient must be made aware of this fact and of the resulting temporal and logistical requirements, or else compliance may be impaired. AMD is a chronic disease in which the responsible pathogenetic-mechanistic cascade cannot be brought to a standstill with causally directed treatment early on in the course of illness, even in the stages for which effective treatment is available. Rather, its course can be positively affected only by treatment that is given intensively and consistently over a long period of time.

There are a variety of established strategies for anti-VEGF therapy in exudative AMD. The treatment approach that was first tested in clinical trials consisted of regular once-monthly administration of VEGF inhibitors. Each administration is an intravitreal injection and thus an ambulatory surgical procedure; there is an associated risk of ca. 0.029% per injection (roughly 1:3500) of severe intraocular infection (endophthalmitis) (e11). Endophthalmitis is usually treated with vitrectomy and intraocular antibiotics. The visual outcome after endophthalmitis is highly variable and often poor, depending on the aggressiveness of the responsible pathogen. and on other factors (e12). Other rare, but clinically relevant risks of intravitreal therapy include sterile inflammatory reactions (0.09–2.9%) (e13) and, very rarely, retinal detachment (0.013%) (e14).

In subsequent efforts to tailor the treatment to the requirements of each individual patient, the need-adapted "pro re nata" and "treat and extend" treatment strategies were developed. These are now used at most centers where AMD is treated, in preference to the original, regularly scheduled monthly injections. The two strategies differ in the details, but both are designed to ensure that patients receive the optimal number of injections for their own individual needs. Multiple clinical trials have shown that most patients require ca. 7–8 injections in the first year of treatment to control exudative AMD effectively (37, 38), with fewer injections generally being needed in later years. Studies on real-life care in Germany have shown that patients are at greater risk of receiving too few injections than of receiving too many (39, 40). In actual practice, the intervals between treatments tend not to be optimal because of a variety of factors, including comorbidities, logistical difficulties in transporting the patient to outpatient appointments, etc. It has been found in numerous studies that phases in which treatment is not

Lifestyle changes

Smoking cessation is recommended to patients in all stages of AMD to prevent the emergence or progression of the disease. Dietary supplements have smaller effects and are only effective in certain stages of AMD.

Intravitreal anti-VEGF therapy

Four such drugs are now available, one of them off-label (bevacizumab, in use since 2005) and three that have been approved for use in Europe: ranibizumab (approved 2007), aflibercept (approved 2012), and brolucizumab (approved 2020).

given often enough are often associated with irreversible vision loss. It is, therefore, an important therapeutic goal to ensure the uninterrupted treatment of the patient. Depending on the degree of activity of the disease, the proper management consists of an intravitreal injection and/or a follow-up visit with visual acuity measurement, funduscopic follow-up, and OCT (23).

In summary, it can be concluded that the current mode of treatment of the exudative form of late AMD, even though it is not directed at the underlying etiology of the disease, nonetheless effectively preserves visual acuity in many patients. The visual acuity has been found to remain stable in more than 70% of treated eyes, while just under 20% actually improve in visual acuity markedly after the initial treatments (38). Anti-VEGF therapy is ineffective, however, in the early, intermediate, and atrophic late stages of AMD. It is thus very important that the subtype of AMD present in each individual eye be properly diagnosed, so that timely treatment can be initiated in those who have exudative late AMD—if at all possible, before the disease has led to irreversible visual loss.

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Atrophic late AMD

No evidence-based treatment for atrophic late AMD is yet available, but a number of treatment approaches are being studied in clinical trials.

Treatment of exudative late AMD

Exudative late AMD is treated with intravitreally injected anti-VEGF drugs. Most patients need more than one injection, typically 7 or 8 injections, in the first year of treatment.

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/lit2920

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Only one answer is possible per question. Please select the answer that is most appropriate

Question 1

To what extent is AMD responsible for vision loss and blindness?

a) The prevalence of AMD has decreased in recent years.
b) AMD mainly affects persons aged 50 to 60.
c) In Germany, AMD is one of the most common causes of blindness and severe visual impairment.
d) AMD is increasingly becoming an important cause of vision loss and blindness in younger individuals.
e) The prevalence of AMD is negatively correlated with age.

Question 2

What are the main risk factors for AMD?

a) age, smoking, genetic predisposition
b) arterial hypertension, obesity, diabetes mellitus
c) sex, ethnic origin, refractive error
d) UV light exposure, eating habits, lack of exercise
e) alcohol consumption, past eye surgery, raised intraocular pressure

Question 3

What are the stages of AMD?

a) preproliferative, proliferative, and atrophic stages
b) early, intermediate, and late stages; the late stage has two forms, exudative and atrophic
c) incipient, advancing, and mature stages
d) angiogenic early stage, neurodegenerative intermediate stage, cicatricial late stage
e) segmental, focal, and panretinal stages

Question 4

What symptom is typical of advanced AMD?

a) glare sensitivity
b) short-sightedness
c) painful eye
d) distorted vision
e) nocturnal blindness

Question 5

What is the morphological correlate of visionloss due to AMD?

a) corneal opacification
b) altered refractive index of the lens
c) opacification of the vitreous body
d) retinal changes
e) axon loss in the optic nerve

Question 6

What diagnostic technique is suitable for the detection of active leakage from pathological blood vessels in exudative AMD?

a) optical coherence tomography
b) visual acuity test
c) visual field examination
d) fluorescein angiography
e) tonometry

Question 7

What lifestyle change is explicitly recommended to patients with AMD?

a) smoking cessation
b) alcohol abstinence
c) vitamin B_1 supplementation
d) weight loss
e) endurance sports

Question 8

How can the atrophic late form of AMD be treated?

a) Lasering of drusen prevents the appearance of atrophic areas.
b) No evidence-based treatment is currently available.
c) Dietary supplements slow the growth of atrophic areas.
d) The injection of neuroprotective drugs leads to the regression of atrophic areas.
e) Lifestyle changes induce the repair of retinal atrophic areas.

Question 9

How can the exudative late form of AMD be treated?

a) with the intravitreal injection of steroids
b) with the surgical excision of the pathological CNV membrane
c) with surgical macular rotation
d) with the intravitreal injection of VEGF inhibitors
e) with retinal laser therapy

Question 10

What are the typical signs of postoperative endophthalmitis?

a) perception of light flashes
b) painful, red eye
c) acute-onset diplopia
d) excessive lacrimation
e) headache, nausea, and vomiting

► **Participation is possible only via the Internet: cme.aerzteblatt.de**

Supplementary material to:

The Diagnosis and Treatment of Age-Related Macular Degeneration

by Andreas Stahl

Dtsch Arztebl Int 2020; 117: 513–20. DOI: 10.3238/arztebl.2020.0513

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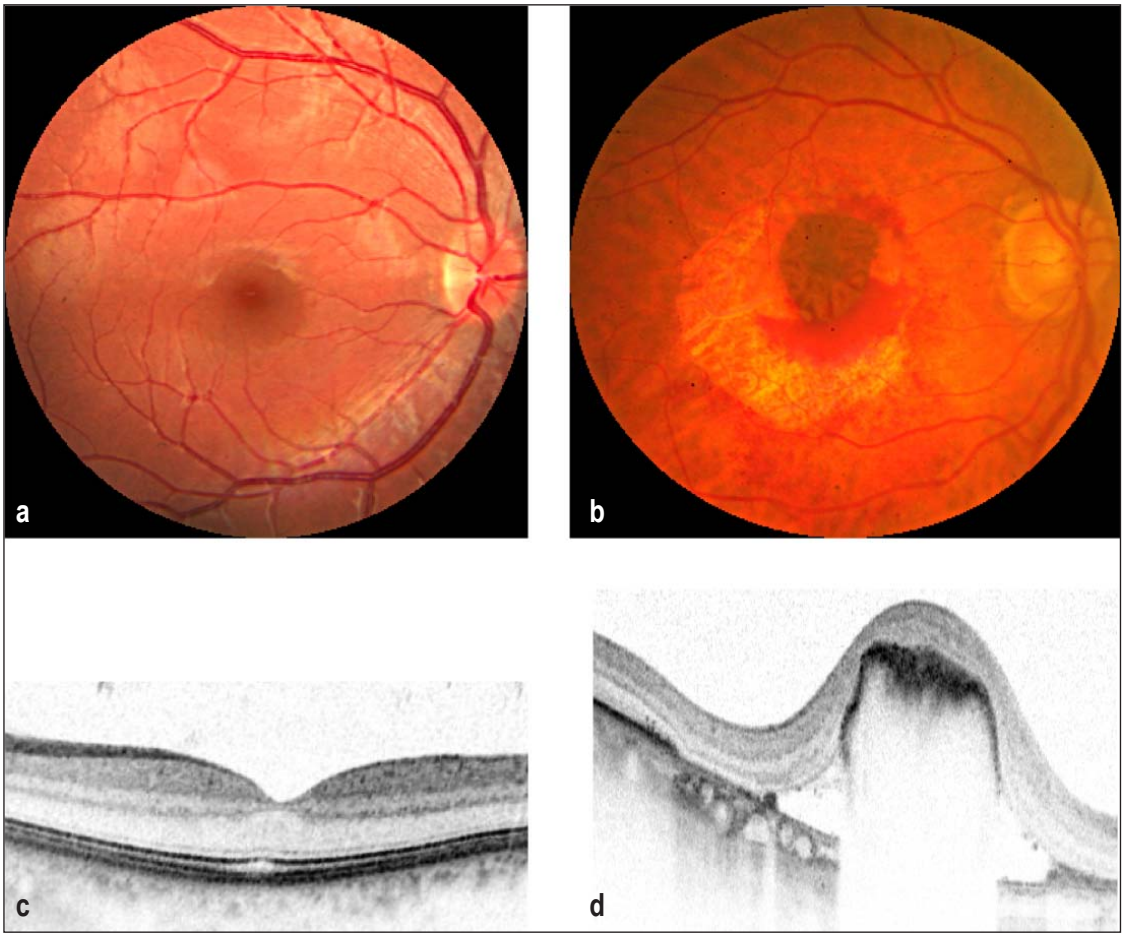
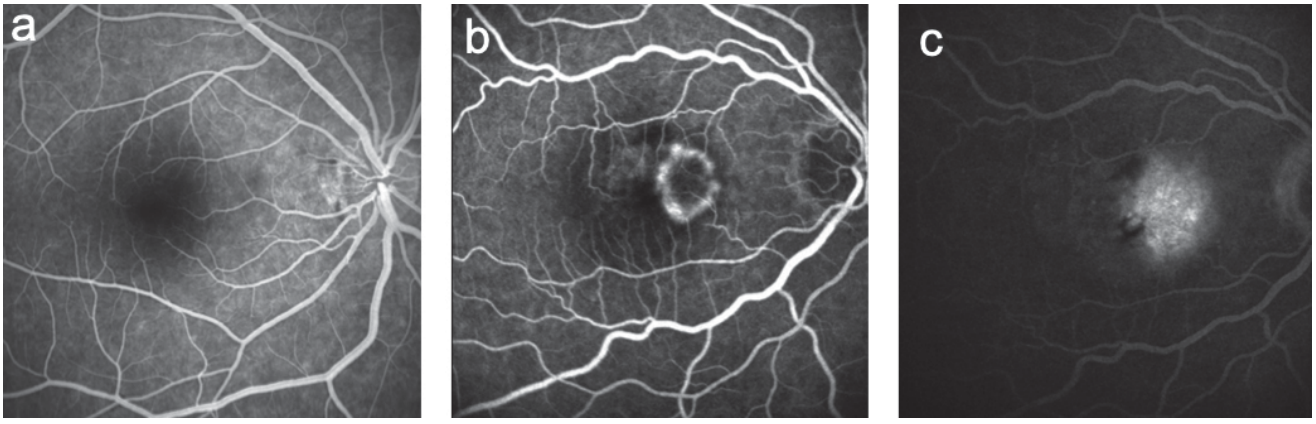


eFigure 1: Normal findings and tear of retinal pigment epithelium in exudative late AMD
Normal findings on funduscopy and optical coherence tomography (OCT) are seen in the images on the left (a, c).
The findings in exudative late AMD are seen in the images on the right (b, d): hemorrhage from a choroidal neovascularization membrane (CNV), along with a tear in the retinal pigment epithelium (RPE). The orderly structure of the retinal layers is disrupted, and central vision is markedly impaired because of hemorrhage and atrophy.



eFigure 2: Fluorescein angiography for the diagnosis of exudative AMD
a) Normal fluorescein-angiographic findings in a healthy macula.
b) A classic CNV membrane in exudative AMD. The pathological vessels are well seen.
c) The angiographic late phase documents marked leakage from the pathological blood vessels of the CNV membrane into the macular parenchyma.
CNV, choroidal neovascularization