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# Morphological and Angiographic Peripheral Retinal Changes in Patients with Age-Related Macular Degeneration

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***Objective:*** To show morphologic and angiographic changes in the peripheral retina in patients with age-related macular degeneration (AMD) using wide-field fundus imaging, and to compare these findings with those from healthy controls.

***Design:*** Cross-sectional clinical study.

***Participants:*** In total, 152 patients with clinical AMD and 150 healthy controls (without AMD in either macula) were studied. Subjects were ≥50 years of age. Exclusion criteria were diabetic retinopathy, previous retinal surgery, high myopia, or dense cataract, as well as any retinal inflammatory, degenerative, or occlusive disease.

***Methods:*** For both groups of patients, color fundus images were captured with the Optos P200 MA camera (Optos, Dunfermline, Scotland). Image analysis software was used to characterize each image. Angiography was performed on the AMD group only. Morphological and angiographic peripheral retinal changes were studied per the frequency of their occurrence, the affected peripheral retina (clock hours), and the localization of peripheral changes with regard to the eye equator. Statistical significance was defined at a level of $P < 0.05$.

***Main Outcome Measures:*** Peripheral changes in both groups according to their type and frequency (percentage of eyes with detected retinal changes), the number of clock hours of affected peripheral retina, and their localization with regard to the equator of the eye.

***Results:*** Drusen, reticular pigmentary changes, and paving stone degeneration occurred more frequently in the AMD group than in controls ($P < 0.001$, $P < 0.001$, and $P < 0.001$ respectively), whereas white without pressure occurred more frequently in the control group ($P = 0.027$). In both groups, peripheral retinal changes were observed peripheral to the equator in more than 40% of analyzed eyes. In control Croatian subjects, peripheral drusen were seen in 38% of subjects compared with 68% of AMD subjects.

***Conclusion:*** Drusen, reticular pigmentary change , and paving stone degeneration occur significantly more frequently in subjects with AMD compared with controls. White without pressure degeneration was present in a high percentage of control subjects. *Ophthalmology Retina 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is the most prominent cause of central visual acuity loss in the population older than 50 years.[1–4] The wet form of AMD is a more serious condition than dry AMD because, if it is not treated, the central visual acuity can be permanently lost within a short time. Therefore, it is important to assess the risk of progression from the dry type to the wet type of the disease.

According to many population studies on AMD prevalence conducted in Norway,[5] Greece,[6] and the United Kingdom,[7] AMD will become more prevalent in the next 15 years due to an increase in the percentage of elderly people in the population.[8]

Recent data suggest that the retinal periphery can exhibit some important morphological changes, such as peripheral drusen and reticular pigmentary changes, which are frequently connected with the wet form of AMD.[3–12]

Disease progression is usually documented using fundus cameras that image only the posterior part of the retina in a single field, which accounts for 45°–50° of the entire retina.[1–21] In those studies, the retinal periphery outside of the central 50° was not visualized nor analyzed, and consequently those results are insufficient to characterize retinal peripheral changes.

In recently published studies,[22–24] wide-field cameras were used in AMD patients mainly to record peripheral retinal changes and their autofluorescence characteristics. However, to our knowledge, few studies if any recorded and analyzed peripheral fluorescein angiographic changes in AMD patients.

The purpose of this clinical study was to compare morphological characteristics of peripheral retinal changes between AMD patients and a healthy control group, and to compare the peripheral retinal changes between the 2 AMD types according to type, frequency, retinal periphery involvement, and localization of observed retinal changes in relation to the equator of the eye.



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## Participants and Methods

### Subject Recruitment

This cross-sectional clinical study included 152 patients with clinical signs of AMD and 150 healthy controls >50 years of age.

Ethics committee approval (EP-7999/11−11) was obtained for procedures used in the study design, which are consistent with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before study participation.

Eligibility for the study in a group of patients with clinical signs of AMD (AMD group) was determined according to international classification of AMD.[3,4] Healthy controls (control group) were participants >50 years of age, without clinical signs of AMD. Exclusion criteria for both groups were diabetic retinopathy, retinal inflammation, degenerative and occlusive diseases, previous retinal surgery, high myopia (>6 drusen), dense cataract, and allergy to medications used in the study, such as sodium fluorescein and mydriatics.

After signing informed consent forms, the medical history, including smoking, kidney function, and allergy to drugs and contrast media, was taken for all participants.

All subjects were examined using biomicroscopy (both eyes) in order to determine lens status in phakic patients according to Lens Opacities Classification System III[25] and in pseudophakic patients according to posterior capsule opacification. Fundus examination was performed using a noncontact handheld lens (66 D) and a slit lamp to determine the presence/absence of AMD clinical signs.

Macular OCT (Cirrus spectral domain; Carl Zeiss, Oberkochen, Germany) and wide-field imaging (Optomap P 200 MA, Optos) were obtained for each subject.

### Wide-field Image Acquisition

All participants had both eyes dilated with mydriatic solutions (mixture of tropicamide 2% and neosynephrine 10%) to facilitate the capture of high-quality images.

Native-color images of each eye included the macular area obtained with the Optos Resmax program, whereas the periphery was scanned with the Optomap Plus program (Optos) to document the upper and lower hemisphere of each fundus.

Fluorescein angiographic (FA) images were obtained with the Optomap FA program (Optos) in the AMD group only. The obtained images were included in the analysis only if they were of high quality and if it was possible to analyze >270° of retinal periphery.

Color and FA images were graded by masked graders for the presence of peripheral reticular pigmentary changes (RPCs); peripheral drusen; hyperpigmented changes, such as nevi and pigmented clumping; and hypopigmented changes, such as atrophic areas or retinal pigment epithelium depigmentation. Other degenerative retinal changes, such as paving stone degeneration (PS), lattice degeneration, white without pressure (WWP), snail tracks, retinoschisis, atrophic holes, neovascularization, synchysis, vitreous opacities, microaneurysms, leakage, and capillary nonperfusion zones were also noted if present.

The observed retinal changes were analyzed according to type, extent as measured in clock hours, and localization of changes with regard to the eye equator. A drusen together (DT) group was divided into 2 subgroups: a dense drusen (D) subgroup with >20 drusen in 1 clock hour of peripheral retina, and a sporadic or rare density drusen (DS) subgroup with <20 drusen in 1 clock hour of peripheral retina. FA images were graded according to the presence of hyper- or hypofluorescence of the observed peripheral retinal changes.

Each participant had both of their eyes analyzed, which means that the 2 eyes shared the same biological environment, so we assumed the findings for those eyes to be similar in our statistical analysis.

All images were analyzed by a special computer scheme, applied on each image, that included superimposing 3 circles to define the posterior pole, the equator, and the periphery of the eye. The first interior (smallest circle) had a diameter of 4 optic disc diameters (DDs) (4 DD = 6000 μm) with the center placed at the fovea, and this demarcated as the posterior pole. The region outside of this circle was regarded as the retinal periphery, which in turn was divided into pre-equatorial (peripheral to the equator), equatorial, and postequatorial regions. The equatorial retina was defined by an annulus made of 2 circles, with center at the optical center of the eye and radii of 7 and 9 DD (Fig 1). All images were reviewed independently by 2 retinal specialists, and their results were compared for consistency.

### Statistical Analysis

The frequency of morphological and angiographic retinal changes in each study group was described by absolute frequency and corresponding percentages, whereas the extent of changes measured in clock hours was described by medians and interquartile ranges (25th and 75th percentiles). Differences in categorical data between the studied groups were analyzed by the chi-square test, whereas differences in quantitative data were analyzed by the Mann−Whitney $U$ test.

Data consistency between 2 retinologists (Z.V., and B.A.D.) was assessed by the κ weight coefficient. A $P$ value <0.05 was considered significant. We used MedCalc Statistical Software, version 12.7.8 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org) for data analysis.

## Results

In accordance with inclusion and exclusion criteria, 152 patients (304 eyes) with clinical signs of AMD and 150 healthy subjects (300 eyes) were enrolled in the study.

In all, 280 AMD eyes and 285 control eyes were deemed suitable for morphological and angiographic analyses. The primary reasons for exclusion of the enrolled eyes in both groups were poor images from cortical cataract (14 AMD eyes, 6 control eyes), from corneal opacification (1 AMD eye, 3 control eyes), or for indeterminate reasons (8 AMD eyes, 3 control eyes). Four patients in the AMD group did not undergo angiography (8 AMD eyes) because of allergy to sodium fluorescein.

In the AMD group, we had 100 female and 52 male patients, with a median age of 76 years; 23 were smokers. The control group comprised 94 female and 56 male participants, with a median age of 74 years; 16 were smokers. There was no statistically significant difference between groups according to gender, age, or smoking habits.

A descriptive and comparative analysis of morphological retinal changes between AMD and control eyes was performed. The numbers of eyes varied somewhat because visualization and analysis were not always possible depending on the peripheral retinal feature being studied.

First, we analyzed a difference in the type and frequency of morphological retinal changes between AMD and control groups (Table 1). Table 1 shows that there are statistically significant differences for DT, D, RPCs, and a group of other degenerative changes (ODs) that included all of the above. Retinal changes were more frequently observed in the AMD group compared with controls ($P < 0.01$ for DT, D, and RPCs and $P = 0.030$ for ODs).

Within the OD group, PS was seen more frequently in the AMD group ($P < 0.001$), whereas WWP and VOs were more frequently observed in the control group (WWP, $P = 0.027$; VO, $P = 0.043$). The extent of observed morphological changes, described in clock