Assessment of macular function by microperimetry in intermediate age-related macular degeneration

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PURPOSE. *To evaluate retrospectively macular function by microperimetry (MP) in intermediate age-related macular degeneration (AMD).*

METHODS. *Thirty eyes of 30 patients with intermediate AMD and a visual acuity of 20/32 or better were enrolled in the study. Macular function in patients with intermediate AMD and age-matched control group were carried out with MP1 microperimeter. Mean sensitivity (MS), mean defect (MD) parameters, fixation patterns, and localizations were evaluated. Mann-Whitney U test was used for the comparison of macular function parameters between the intermediate AMD group and the control group.*

RESULTS. *MS was 12.7±2.8 dB and MD was detected as –6.2±2.2 dB in the intermediate AMD group by MP. Fixation patterns were stable in 22 eyes, relatively unstable in 7 eyes, and unstable in 1 eye. Fixation location was predominantly central in 19 eyes, poor central in 5 eyes, and predominantly eccentric in 6 eyes. In the control group MS was 18.0±0.6 dB and MD was –1.9±0.6 dB. When compared with control group, the decrease in MS and the increase in MD were statistically significant in the intermediate AMD group (p=0.001 and p=0.001, respectively).*

CONCLUSIONS. *Assessment of retinal sensitivity with MP1 microperimeter is a rapid, safe and noninvasive diagnostic method. Early macular function loss in intermediate AMD can be precisely detected by MP1 microperimeter before significant visual impairment is established and it is also useful for demonstrating the shift in the localization and the stability of fixation prior to progression of intermediate AMD to advanced and exudative stage. (Eur J Ophthalmol 2008; 18: 595-600)*

KEY WORDS. *Intermediate age-related macular degeneration, Microperimetry*

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INTRODUCTION

Age-related macular degeneration (AMD) is one of the major causes of severe vision loss associated with increasing age in developed countries (1), and may be classified in two groups as the nonexudative type and the exudative type. Drusen, retinal pigment epithelial (RPE) abnormalities, and geographic atrophy are the clinical features associated with nonexudative AMD. Choroidal neovascularization (CNV) and its consequences like serous sensory retinal detachment, subretinal hemorrhages, and disciform scar are considered as exudative AMD.

The earliest morphologic feature of AMD is the development of drusen, mainly divided into two types as basal laminar deposit and basal linear deposit (2). These deposits are not ophthalmoscopically evident but they may cause retinal dysfunction and in some cases angiographic changes as faint staining in the late phases (3). Clinically drusen can be divided into hard or cuticular, soft or granular, diffuse or confluent drusen (4). Development of soft drusen is the second major feature of AMD (2, 3). Soft drusen are round yellow lesions with ill-defined borders that tend to coalesce and become confluent.

According to The Age-Related Eye Diseases Study

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(AREDS), patients who have one or more large drusen (≥125 µm) or extensive intermediate drusen (≥63 µm, <125 µm) and/or geographic atrophy that does not involve the center of macula with visual acuity 20/32 or better and no advanced AMD in either eye are classified as intermediate AMD (1). MP1 microperimeter is a newly introduced automatic fundus perimeter that has been shown to be effective for assessing macular function in several macular pathologies (5-11). The aim of this study is to evaluate retrospectively the central retinal function by MP1 microperimeter in patients with intermediate AMD.

METHODS

Patients being followed in the Yeditepe University Eye Hospital with the diagnosis of intermediate AMD were enrolled in the study. Eyes with visual acuity 20/32 or better were evaluated. An informed consent was obtained from all of the patients, and all tenets of the Declaration of Helsinki were followed. Inclusion criteria were regarded as the presence of one or more large drusen (≥125 µm), or extensive intermediate drusen (≥63 µm, <125 µm), and/or geographic atrophy that does not involve the center of macula. Eyes with geographic atrophy involving the center of macula, CNV, significant media opacity, glaucoma, previous laser treatment, any other retinopathy, and any refraction error ≥ ±6 diopters were excluded. Complete ophthalmic examination followed by fundus fluorescein angiography and optical coherence tomography (Stratus-OCT, Carl Zeiss Meditec Inc., CA, USA) were performed. The ophthalmic examination involved best-corrected visual acuity determination, anterior segment evaluation, intraocular pressure detection by applanation tonometer, and a detailed fundus examination. Only one eye of each participant that was randomly selected was recruited in the study.

Macular function in patients with intermediate AMD and age-matched control group was examined with a novel automatic fundus-related perimeter (MP1 Microperimeter, Nidek Technologies, Italy). After a pupillary dilation of at least 6 mm with tropicamide 0.5%, all patients were adapted to dark for 15 minutes. Once the patient was seated comfortably, the fellow eye was patched. All examinations were performed by one experienced examiner under the standardized light conditions with the room lights off. For each participant, a pre-test training examination was also performed.

MP-1 performs automatic fundus perimetry using an electronic eye-tracking system with a refraction correction system for errors between –12.5 and +6 diopters. The working distance is set at 47.1 mm (12). The fundus is imaged on a video monitor with an infrared fundus camera at a resolution of 1392 × 1038 pixels and the field of view is 45 degrees (5, 6, 12). An internal liquid crystal display (6.5" LCD, 640 × 640 pixels) acts as the projection system. The fixation target and stimuli are projected onto retina by LCD monitor.

A red cross as the fixation target of 1° diameter, a white monochromatic background at 4 asb, a Goldmann III size of stimulus with 200 ms projection time, and a customized radial grid of 76 stimuli covering central 20° that was centered onto the fovea were the parameters utilized for MP examination of a 4-2 double-staircase strategy. During examination, a stimulus was projected onto the patient's blind spot at 60 sec, allowing the examiner to check the patient's reliability. At the end of each examination, a color fundus photograph was acquired. The color fundus photograph was then aligned with the infrared image, so that results were automatically overlapped onto the color fundus image.

Mean sensitivity (MS) and mean defect (MD) parameters were assessed and results were reported in decibels. Macular function in patients with intermediate AMD and age-matched control group were evaluated retrospectively. In addition, fixation patterns and fixation localizations were assessed by MP. Fixation localization was classified as predominantly central, poor central, and predominantly eccentric fixation. Fixation stability was graded as stable, relatively unstable, and unstable.

Mann-Whitney *U* test was used for the comparison between the intermediate AMD group and the control group. SPSS version 11.0 system for personal computer was used for all statistical analyses and $p<0.05$ was regarded as statistically significant.

RESULTS

Thirty eyes of 30 patients (14 female, 16 male) ranging between 55 and 81 years of age (mean 67.7±7.3 years) were enrolled in the study. Mean visual acuity was found to range between 20/32 and 20/20. Central macular thickness was 198.1±21.6 µm (ranging between 149 µm and 236 µm) detected by OCT. OCT revealed RPE layer irregularities, thickened hyperreflective lesions secondary to

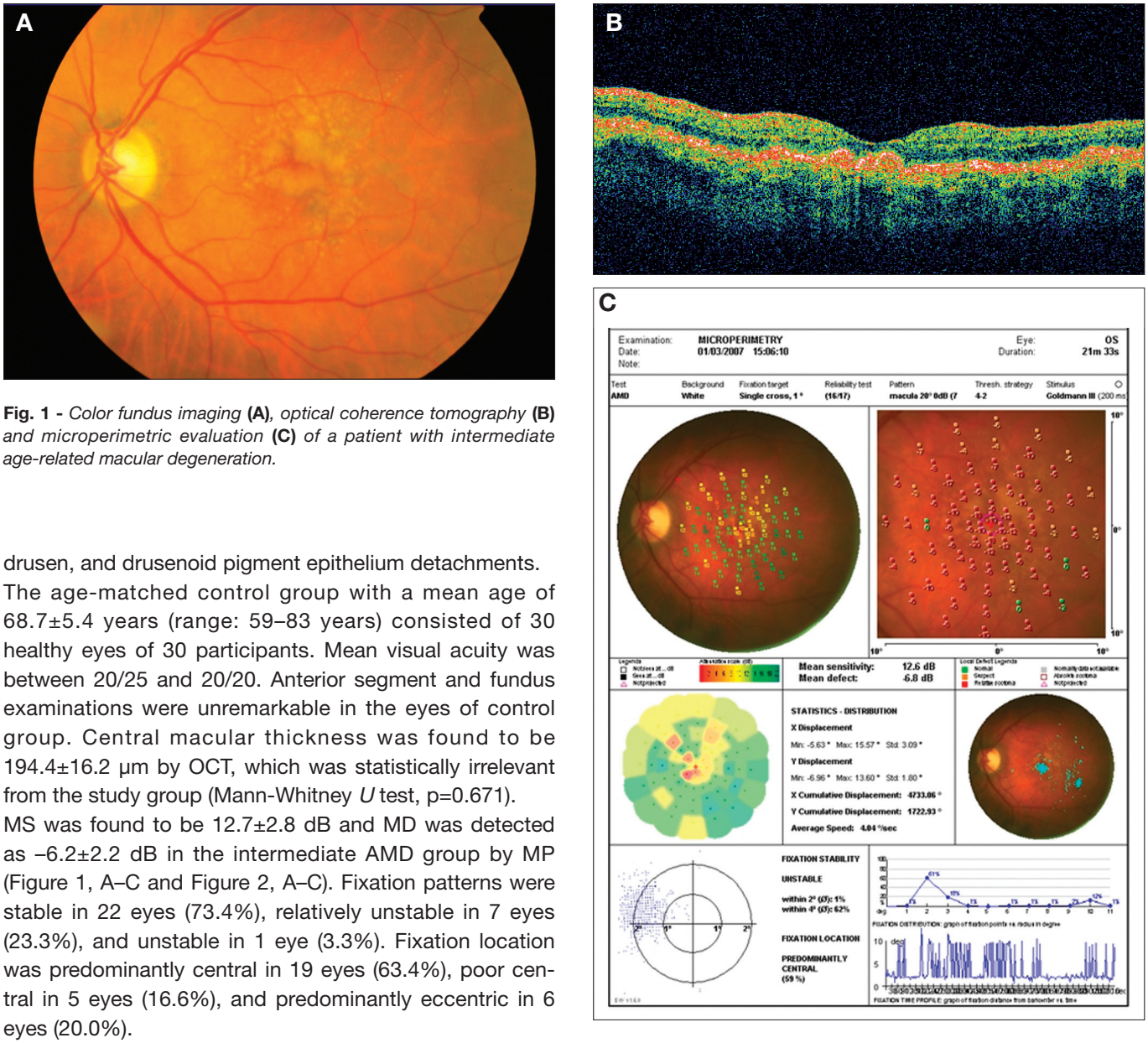


Fig. 1 - *Color fundus imaging* **(A)**, *optical coherence tomography* **(B)** *and microperimetric evaluation* **(C)** *of a patient with intermediate age-related macular degeneration.*

drusen, and drusenoid pigment epithelium detachments.

The age-matched control group with a mean age of 68.7±5.4 years (range: 59–83 years) consisted of 30 healthy eyes of 30 participants. Mean visual acuity was between 20/25 and 20/20. Anterior segment and fundus examinations were unremarkable in the eyes of control group. Central macular thickness was found to be 194.4±16.2 µm by OCT, which was statistically irrelevant from the study group (Mann-Whitney *U* test, p=0.671).

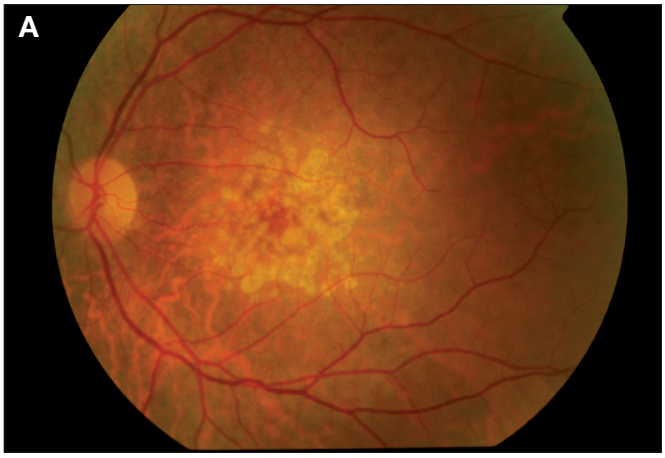
MS was found to be 12.7±2.8 dB and MD was detected as –6.2±2.2 dB in the intermediate AMD group by MP (Figure 1, A–C and Figure 2, A–C). Fixation patterns were stable in 22 eyes (73.4%), relatively unstable in 7 eyes (23.3%), and unstable in 1 eye (3.3%). Fixation location was predominantly central in 19 eyes (63.4%), poor central in 5 eyes (16.6%), and predominantly eccentric in 6 eyes (20.0%).

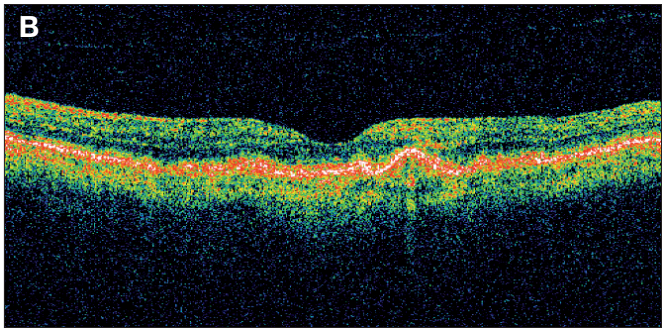
In the control group MS was 18.0±0.6 dB and MD was –1.9±0.6 dB. Fixation patterns were stable in 29 eyes (96.7%) and relatively unstable in only 1 eye (3.3%). Fixation location was predominantly central in 28 eyes (93.4%) and poor central in 2 eyes (6.6%). No predominantly eccentric location or unstable pattern of fixation was encountered during MP evaluation in the control group.

When compared with control group, the decrease in MS and the increase in MD were statistically significant in the intermediate AMD group (Mann-Whitney *U* test, p=0.001 and p=0.001, respectively).

DISCUSSION

Non-exudative AMD accounts for approximately 25% of severe vision loss from AMD (13). Recently AREDS Group developed a simplified clinical scale defining risk categories for the development of advanced exudative AMD (14). The scoring system developed for patients assigned to each eye one risk factor for the presence of one or more large drusen and one risk factor for the presence of any pigment abnormality. Risk factors were summed across both eyes, yielding a 5-step scale (0–4) on which





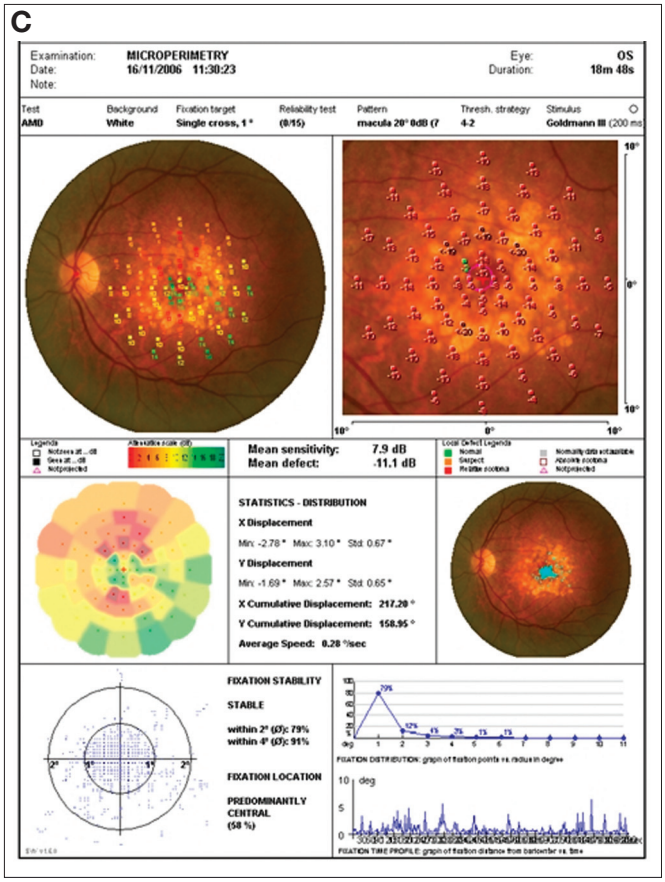


Fig. 2 - *Examples of color fundus imaging* **(A)***, optical coherence tomography* **(B)***, and microperimetric evaluation* **(C)** *of another patient with intermediate age-related macular degeneration.*

the approximate 5-year risk of developing exudative AMD in at least one eye increased in the following sequence: 0 factors, 0.5%; 1 factor, 3%; 2 factors, 12%; 3 factors, 25%; and 4 factors, 50% (14). Nevertheless, there is no well established treatment to preserve or improve visual acuity in non-exudative type of AMD. The only proven therapy is the use of vitamin supplements (15, 16). AREDS showed that supplemental antioxidants (500 mg of vitamin C, 400 IU of vitamin E, 15 mg of beta-carotene) and 80 mg zinc plus 2 mg copper were effective to significantly retard the progression of intermediate AMD to advanced AMD by 25% over 5 years (16).

Determination of visual acuity in macular disorders and especially in AMD is insufficient for assessing functional vision. Conventional central visual field testing is not always effective since generally accurate results cannot be obtained because of unstable or extrafoveal fixation in patients with AMD. Short wavelength automated perimetry (SWAP) was used for determination of macular sensitivity. SWAP isolates the short wavelength sensitive cone response by suppression of other cone types using a yellow background by standard Humphrey perimeter (17, 18). In a prospective trial, mean retinal sensitivity detected by SWAP in central 10 degrees was found significantly lower in eyes with soft drusen than those without, whereas there were no differences in visual acuity (17).

A novel technique of fundus perimetry known as microperimetry allows the clinician to evaluate macular function quantitatively. Moreover, microperimetry detects the location and the stability of retinal fixation. Scanning laser ophthalmoscope (SLO) microperimetry was the first technique of fundus perimetry (19-21); however, fully automatic examinations and follow-up examinations using the identical previous points tested were not available. The recently developed MP1 microperimeter performs automatic perimetry and follow-up examinations over the same retinal points tested independent of fixation characteristics while compensating eye movements during the examination (22).

Midena and colleagues compared microperimetry findings and fundus autofluorescence in 13 eyes of patients

with early AMD (23). Their results revealed decreased macular sensitivity over large drusen, pigment abnormalities, and areas of increased autofluorescence. The authors demonstrated a more relevant decrease in sensitivity corresponding to areas of large drusen than pigment abnormalities and smaller drusen. The authors suggested the use of MP and fundus autofluorescence together for monitoring AMD progression (23).

Likewise, when microperimetry findings of intermediate AMD patients were evaluated, our results demonstrated a noteworthy decrease in macular sensitivity when compared to the control group. Mean sensitivity significantly decreased and mean defect remarkably increased in the intermediate AMD group (Mann-Whitney *U* test, p=0.001). The patients diagnosed with intermediate AMD enrolled in the present study had no or moderate loss of visual acuity. Detection of macular dysfunction even in the absence of significant visual loss can be attributed to the degeneration of retina pigment epithelium cells and consequently photoreceptors (24, 25). A correlation between the presence of drusen and photoreceptor cell death in the retinas of eyes diagnosed with AMD was previously reported (25). MP1 microperimetry seems to be useful for detection of central macular sensitivity loss even before the development of exudative AMD.

Microperimetric evaluation is also functional for demonstrating and better understanding the shift in the localization of fixation before progression of intermediate AMD to advanced stage. Decrease in fixation stability and central fixation loss are among the characteristics of central visual function deterioration in neovascular AMD. At the terminal stage eccentric fixation and unstable fixation develops especially with the longer duration of CNV (5, 26). Our findings revealed a predominantly central and stable fixation in the majority of the study group. However, unstable fixation and extrafoveal fixation characteristics were also detected in some of our patients. These changes must be taken into consideration in intermediate AMD patients before CNV arises. Johnson and colleagues reported that the changes in adjacent photoreceptor cells were dependent on the size of underlying drusen (24). The increase in drusen size also increased the loss of outer segment loss of photoreceptors, the reduction in the thickness of outer nuclear layer, and the changes in synaptic cytoarchitecture over large drusen (24). Even small, subclinical drusen (<63 µm lateral spread) might impact photoreceptor morphology, as evidenced by the deflection of both inner and outer segments and by decreased outer segment length (24). Also, Johnson and colleagues found a reduction of approximately 30% in the number photoreceptors over drusen (27). These data support our results that microperimetry might demonstrate functional macular deterioration not only as impaired retinal sensitivity but also as loss of central fixation and decreased fixation stability, even in eyes with intermediate AMD having near normal visual acuity.

Assessment of retinal sensitivity with MP1 microperimeter is a rapid, safe, and noninvasive diagnostic procedure. MP1 microperimeter is effective for detection of early macular function loss in patients with intermediate AMD when compared with an age-matched control group, allowing quantification of retinal threshold and scotoma characteristics with the assessment of the location and stability of retinal fixation. Further prospective and controlled studies having greater sample sizes are necessary to evaluate the retinal function in AMD especially for monitoring the risk of progression of intermediate AMD to advanced and exudative stage.

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