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Microperimetric evaluation in eyes with cuticular drusen

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Article

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Abstract

Introduction: To determine microperimetric retinal sensitivity in patients with cuticular drusen and evaluate differences on retinal sensitivity according to cuticular drusen type on spectral domain optical coherence tomography (SD-OCT) scans.

Methods: Thirty two eyes of 52 participants with cuticular drusen were recruited in this retrospective cross-sectional study. All subjects underwent ophthalmologic evaluations including best-corrected visual acuity (BCVA) assessment, SD-OCT, slit-lamp biomicroscopy, color fundus photography, fluorescein angiography, fundus autofluorescence, and mean retinal sensitivity (MRS) as measured by microperimetry, which was performed using 52 stimulus points. The division of patients into three groups was based on SD-OCT. The correlation between MRS and the mean deviation (MD) value was evaluated with linear regressions.

Results: MRS was significantly different between cuticular drusen types (p<0.05). Generalized decreased MRS was detected more frequently in eyes with cuticular drusen type 2 (73.7%, 14/19) and 3 (85.7%, 18/21) compared to normal eyes. Retinal sensitivity was significantly correlated only with the MD value (p<0.001). There were no significant correlations with age, corrected visual acuity, pattern standard deviation, drusen occupying points, or cuticular drusen types.

Conclusion: Our study showed that MRS decreased according to the type of cuticular drusen on SD-OCT. These visual function tests could be useful measurements, for cuticular drusen type.

Precis

The mean retinal sensitivity decreased according to the type of cuticular drusen on spectral domain optical coherence tomography. These visual function tests could be useful measurements, especially in terms of cuticular drusen type.

Introduction

Cuticular drusen are characterized by fundus features that include uniform small, yellow densely clustered sub-retinal pigment epithelium (RPE) lesions, and are a separate subtype of age-related macular degeneration (AMD).[1] Cuticular drusen are present between the basal lamina of the RPE and the inner collagenous layer of the Bruch's membrane.[2,3] Unlike general drusen, which are similar to reticular pseudodrusen (RPD), cuticular drusen are not limited to the macula; however, they are widely located outside the arcade. Based on these features, cuticular drusen are categorized into three patterns according to the morphologic features observed using spectral domain optical coherence tomography (SD-OCT).[4]

Although visual acuity is a principle means of representing visual function, visual acuity was not adequately associated with contrast sensitivity in eyes with large soft drusen in an AMD trial.[5] Rather,

visual function tests, including microperimetry and multifocal electroretinography, have been demonstrated to be important attributes in the performance of activities used in the daily life of patients with AMD,[6–8] since patients with AMD often complain of problems and vision loss under low lighting, low contrast, and changing light conditions despite possessing good visual acuity.[9,10]

Full-field electroretinogram responses were reportedly more reduced in the diffuse RPD distribution type.[11] Microperimetry is effective in the detection of functional changes in the early and advanced stages of AMD.[12–14] However, whether microperimetry is more effective as a functional measure in patients with cuticular drusen has not been determined. Information on the relationship between cuticular drusen and retinal function has been limited and further investigation is warranted.

This study aimed to examine the influence of cuticular drusen on retinal and visual function using microperimetry. Moreover, this retrospective study sought information on visual function in eyes with cuticular drusen using multiple testing modalities to evaluate the correlations of the test results with other parameters, such as age and drusen type.

Methods

Patient selection

Patients with cuticular drusen were included in this retrospective cross-sectional study from May 2020 to March 2021 at the Hangil Eye Hospital. All eyes were classified based on the characteristics of the cuticular drusen phenotype using four imaging methods: color photography, SD-OCT (Eye Explorer Version 1.10.4.0; Heidelberg Engineering, Heidelberg, Germany), fluorescein angiography (FA, Spectralis, Heidelberg Engineering), and fundus autofluorescence (FAF, Optos California 200DTx with an angular range of approximately 200° horizontally and 170° vertically, Optos, Dunfermline, United Kingdom) using established criteria[4]. The exclusion criteria were presence of neovascular AMD in the study eye, presence of atrophy in the study eye, eyes with reticular pseudodrusen, any ophthalmologic conditions that affect the diagnosis of cuticular drusen or AMD (e.g., any laser scars, retinal detachment, diabetic retinopathy, hypertensive retinopathy, central serous chorioretinopathy, and retinal vein occlusion), history of glaucoma, history of ocular inflammation in the study eye, and incomplete examination.

Multimodal imaging methods

All the patients underwent a complete ophthalmologic examination, including measurement of the best-corrected visual acuity (BCVA), SD-OCT, slit-lamp biomicroscopy, color fundus photography, FA, FAF, and compass fundus perimeter (CMP).

SD-OCT line and raster scans positioned at the fovea were conducted on all study eyes using enhanced depth imaging protocols. The raster scan image comprised 31 B-scans, each consisting of 768 A-scans, 9.0 mm in length, and spaced 240 mm apart, covering a 30° × 25° area. The automatic real-time mode using the eye-tracker system was activated, with a total of 25 frames averaged for one B-scan image. We

differentiated RPDs that deposit above the RPE from cuticular drusen using multimodal images, especially SD-OCT. The morphologic features of cuticular drusen observed on SD-OCT B-scans can be broadly categorized into three patterns[4]: type 1, a shallow elevation of the RPE-basal laminar band, with drusen internal contents difficult to discern; type 2, a drusen of triangular morphologic characteristics resulting in a saw-tooth appearance and hyporeflective internal contents; and type 3, a broad, mound-shaped elevation of the RPE-basal laminar band with hyporeflective internal contents.[4] If classification into one type was difficult owing to existence of a mixed type of cuticular drusen in one eye, which pattern was classified as an advanced type.

Mesopic microperimetry was subsequently performed following pupillary dilation with 1 drop of 1% tropicamide and 2.5% phenylephrine. Retinal sensitivity assessment was conducted using a microperimeter with eye tracking (CMP; centerVue, Padua, Italy) after dark adaptation during 30 minutes, which uses a testing grid termed “New Grid,” which contains all 52 locations tested with a 24 − 2, only one blind spot location, and 12 additional points in the macular region of the visual field (VF). The testing strategy was an adaptation of the Zippy estimation by sequential testing (ZEST).[15] Blind spot responses were monitored by projecting stimuli on the location of the optic nerve head, which were identified manually by the operator on the baseline infrared fundus image captured at the beginning of the test. The mean retinal sensitivity (MRS; arithmetic average of the sensitivities at all locations) of each test was calculated. VF examinations were considered reliable if the false-positive frequency was ≤ 18%.[15] Normative data,[15] used to calculate mean deviation (MD) and MRS and their normative limits, were composed of the same set of healthy participants. The test-retest reliability of microperimetry using CMP was within 95% limits of agreement for sensitivities.[15] Since CMP enables wide-field (30°) VF assessment, CMP was selected as a measure of retinal sensitivity in eyes with cuticular drusen, which are widely distributed on the fundus.

Statistical analysis

Data were analyzed using the paired t-test at each point (52 points) in eyes with types 1, 2, and 3, and compared with normal controls. A one-way ANOVA test was used when there were significant differences between the groups. The Shapiro-Wilk test was used for normality among the groups. The location of each of the 52 values was then assessed to determine whether they were located over the cuticular drusen areas or over areas with no visible pathologic alterations. The mean values of all 52 values were calculated separately for each eye and then separately for the two structural categories. The Mann-Whitney U test was used to compare the classifications under the two different categories. For the analysis of risk factors, each parameter was first entered into the model in a univariate analysis, and parameters found to be statistically significant were then entered into linear regression with a multivariate analysis. All statistical analyses were conducted using SPSS software (version 25.0; IBM, Armonk, NY).

Results

A total of 72 eyes from 43 patients were included in the study. Among them, 20 eyes from 11 patients were excluded because only one or two imaging methods demonstrated cuticular drusen phenotypes or poor image quality. A total of 52 eyes from 32 participants underwent all the study assessments. The demographic and clinical features of the participants are summarized in Table 1. The mean age was 65.7 ± 7.2 years (median, 66.0 y; range, 45–77 y; $p = 0.481$, Shapiro-Wilk test, normal distribution) and 21/32 (65.6%) patients were female. The database used for the normal control group is presented in article[15] reporting 444 healthy participants with a mean age of 48 ± 16 y (Table 1).

BCVA was 0.1 ± 0.1 logMAR (median, 0.05 logMAR; range, 0.0–0.22 logMAR). Visual acuities were not normally distributed ($p < 0.001$, Shapiro-Wilk test).

The average mean sensitivity in the normative data is depicted in Fig. 1A.[1] The distributions of type 1 (Fig. 2), type 2 (Fig. 3), and type 3 (Fig. 4) were 23.1% (12/52), 36.5% (19/52), and 40.4% (21/52) of the eyes, respectively (Table 1).

Table 1
Summary of Clinical and Demographic Features

Features	**Data (Mean ± Standard Deviation)**		
No. of eyes	52		
No. of patients	32		
Women	21		
Age (yrs)	65.3 ± 7.7 (45–77)		
BCVA (logMAR)	0.1 ± 0.1 (0.0-0.2)		
Ocular exams			
Compass fundus perimeter			
Pupil size	4.6 ± 1.1 (2.4–6.2)		
Mean deviation (dB)	-3.7 ± 4.3 (-23.38 - +0.58)		
Pattern standard deviation (dB)	3.4 ± 2.7 (1.23–10.97)		
False positive (%)	0.2 ± 1.5% (0–11)		
Drusen occupying points (total 52)	36.2 ± 15.2		
SD OCT	Type 1	Type 2	Type 3
No. of eyes (%)	23.1% (12/52)	36.5% (19/52)	40.4% (21/52)
Age (yrs)	65.6 ± 5.4	63.2 ± 8.3	68.0 ± 6.8
BCVA (logMAR)	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.2
Mean deviation (dB)	-1.8 ± 2.1	-3.2 ± 3.2	-5.1 ± 5.3
Pattern standard deviation (dB)	2.3 ± 1.0	2.8 ± 7.6	4.0 ± 3.0
Drusen occupying points	40.2 ± 10.5	38.0 ± 16.4	31.0 ± 16.6
Mean Retinal Sensitivity (dB)	**25.1 ± 4.6 ***	**23.9 ± 6.2 ***	**21.3 ± 8.1 ***

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; No. number; SD-OCT = spectral domain optical coherence tomography.

Continuous variables are reported as mean values ± standard deviation (range). All other data are numbers.

Bold indicates statistical significance. $p < 0.05$

*One-way ANOVA test

Evaluation of visual function measures between the types

Table 2 shows the mean retinal sensitivities for each type. In eyes with cuticular drusen, the MRSs of type 1, type 2, and type 3 eyes were 25.1 ± 4.6(dB), 23.9 ± 6.2(dB), and 21.3 ± 8.1(dB), respectively, and shows a tendency to decrease based on the type. The MRS in eyes with cuticular drusen was significantly lower in type 2 (73.7%) and type 3 (85.7%) eyes than in normal eyes, except for five and three eyes, respectively (all $p < 0.001$ for 52 locations, except 0.17, 0.07, 0.33, 0.38, 0.08, 0.54, 0.36, and 0.13 with paired t-test; Table 2). There were significant differences in MRS between types of cuticular drusen ($p < 0.05$, one-way ANOVA, Table 1).

Table 2
Mean Retinal Sensitivity in Normal Eyes vs. Eyes with Cuticular Drusen in Each Group

	Type 1 (n = 12)	**Type 2 (n = 19)**	**Type 3 (n = 21)**
Normal (n = 444)	26.6 ± 5.4	26.6 ± 5.4	26.6 ± 5.4
Cuticular Drusen (n = 52)	25.1 ± 4.6	23.9 ± 6.2	21.3 ± 8.1
P*	**P < 0.05 (6/12 ,50%)**	**All P < 0.05 (except 5 eyes, 73.7%)**	**All P < 0.05 (except 3 eyes, 85.7%)**

Values are mean ± standard deviation (dB) unless otherwise indicate.

Bold indicates statistical significance.

*paired t-test

Evaluation of visual function measures between cuticular drusen and non-cuticular drusen areas

Of these 52 test points, a mean number of 37.5 ± 13.8 test points were confined to areas with cuticular drusen, and 16.5 ± 13.8 points had no visible pathologic multiple yellow spots (non-cuticular drusen areas). Since the values are different at each of the 52 points in the mean normal healthy data, it is reasonable to compare each point by subtracting patient data from normal data. There was no significant difference between cuticular drusen areas (mean, 26.9 dB) and non-cuticular drusen areas (mean, 35.0 dB) (all $p > 0.05$, Mann-Whitney U test) (Fig. 1A-D).

Relationship between variables and visual function tests

In the univariate linear regression, age, corrected visual acuity (CVA, logMAR), MD values, pattern standard deviation (PSD) values, and cuticular drusen type were associated with MRS (all $p \leq 0.05$) (Table 3). Among the factors, only MD values were significantly correlated with MRS ($p < 0.001$) in the multivariate linear regression analysis. The MD values from microperimetry were strongly positively

correlated with MRS (r = 0.975, $p < 0.001$), indicating that eyes with cuticular drusen and lower MD values had a greater decrease in MRS. However, there was no effect on visual acuity ($p = 0.087$).

Table 3
Linear Regression of the Variables Against Mean Retinal Sensitivity

	Univariate Regression		Multivariate Regression	
	β coefficient	*P* *	β coefficient	*P* *
Age (years)	-0.358	**< 0.001**	-0.072	0.062
BCVA (logMAR)	-0.355	**0.001**	-0.072	0.087
Mean deviation	0.928	**< 0.001**	0.826	**< 0.001**
Pattern Standard deviation	-0.399	**< 0.001**	-0.065	0.227
Drusen area (pixcel)	-0.034	0.866		
Drusen occupying points	0.313	0.111		
Cuticular drusen types	-0.310	**0.005**	-0.020	0.584

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.

Overall $R^2 = 0.944$

Discussion

In this study, generalized decreased MRS was detected more frequently in eyes with cuticular drusen type 2 (73.7%, 14/19) and type 3 (85.7%, 18/21) than in normal eyes. As mentioned earlier, since types 2 and 3 have hyporeflective internal contents,[4] relatively elevated drusen over the RPE-basal laminar band render outer segments non-reflective[13] compared to type 1 cuticular drusen on SD-OCT. Histopathologically, drusen over retinal cells exhibit structural and molecular abnormalities suggestive of photoreceptor degeneration and Muller glial activation, implying that the photoreceptor cell function is compromised owing to drusen formation.[16] Similarly, Curcio et al. reported that photoreceptor morphology was disturbed over subretinal drusenoid deposit formation, manifesting as outer segment shortening and loss with inner segment deflection and absence.[17]

Referring to these reports, our results suggest that when the drusen are elevated enough to deform the RPE shape, the overall retinal sensitivity is lowered.

This is further reinforced by the use of microperimetry as a subjective measurement of retinal sensitivity at the mesopic adaptation level, which may be arbitrated by both rod and cone photoreceptors.[8] Retinal sensitivity measured by microperimetry strongly correlates with photoreceptor band integrity on high-resolution OCT imaging in AMD, which is consistent with the damage primarily to the outer retina.[12,18,19]

By applying these results to our study, it appears that as the type of cuticular drusen increases, the height of the drusen increases, which results in RPE deformation, leading to lower MRS in microperimetry.

Several reports have suggested that impaired scotopic and mesopic sensitivity are spatially correlated with the occurrence of large soft drusen or reticular pseudodrusen,[20–24] whereas other studies have reported poor association between the distribution of lesions and loss of retinal sensitivity.[25,26]

In this report, we did not find a significant association between microperimetric sensitivity and the presence or extent of cuticular drusen. Acton et al. revealed that in locations with visual field defects compared to locations without defects, the outer segment layer was thinner in defect locations.[13] Iwama et al. also reported that retinal sensitivities within an area with an irregular ellipsoid zone were significantly lower than those within intact retina in eyes with confluent soft drusen.[26]

From these results, our findings suggest that not all cuticular drusen lesions had an effect on exceeding the threshold enough to deform the outer segments; hence, these lesions do not possess decreased retinal sensitivity on microperimetry.

It is noteworthy that a significant correlation between MRS and the type of cuticular drusen was observed in patients with cuticular drusen (r = 0-0.310, $p = 0.005$). Hence, eyes with a lower MRS were correlated with an bigger type of cuticular drusen. The MD value was the only parameter significantly correlated with MRS, which seems to be influenced by age; however, our results demonstrate that it is not influenced by age in multivariate linear regression (Table 3). Therefore, regardless of age, lower MD values on microperimetry in eyes with cuticular drusen suggest an bigger type of cuticular drusen.

The strengths of our study include the first presentation of microperimetric analysis of cuticular drusen. There have been no reports on the differences in retinal sensitivity among cuticular drusen types. In this study, we evaluated the differences of retinal sensitivity for patients with each type of cuticular drusen. Since significant differences in MRS on microperimetry are presented for each cuticular drusen type, this study suggests that determining the type of cuticular drusen on SD-OCT is valuable (Table 1).

This study proves that MRS on microperimetry can be used as a sensitive tool to measure visual quality and is clinically useful. This is the first report to suggest that it can be a useful tool to measure the quality of vision in patients with cuticular drusen, even in those with good visual acuity.

Our study had several limitations. First, normative data from a previously published report[15] were used for the normal control group. Second, inexperience with CMP resulted in a deviated age group (65.7 ± 7.2); however, the age group showed a normal distribution according to the Shapiro-Wilk test ($p = 0.481$). Third, since this was a cross-sectional study, we did not consider that cuticular drusen could remodel with time. Longitudinal studies that evaluate topographical associations could help draw more definitive conclusions on the changes in the outer segment thickness associated with drusen volume and visual function in eyes with cuticular drusen. Nevertheless, this study is the first to demonstrate the significance of microperimetric visual function in patients with cuticular drusen.

In conclusion, our study showed that MRS decreased based on the type of cuticular drusen on SD-OCT. Our findings suggest that these visual function tests might be useful measurements, especially in terms of cuticular drusen type.

Declarations

Financial Support: None

No conflicting relationship exists for any author

Ethics approval and patient consent.

This study was conducted in accordance with the tenets of the Declaration of Helsinki, and was approved by the institutional review board IRB at the Hangil Eye Hospital in Korea. Given the retrospective design of this study and the use of anonymized data, requirements for informed consent were waived by the institutional review board IRB at the Hangil Eye Hospital in Korea.

Data availablility

The datasets generated durning and/or analyzed during the current study are available from the corresponding author on reasonable request. But it has possibility all patients to do not publish this data, it will need to be de- identified.

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Figures

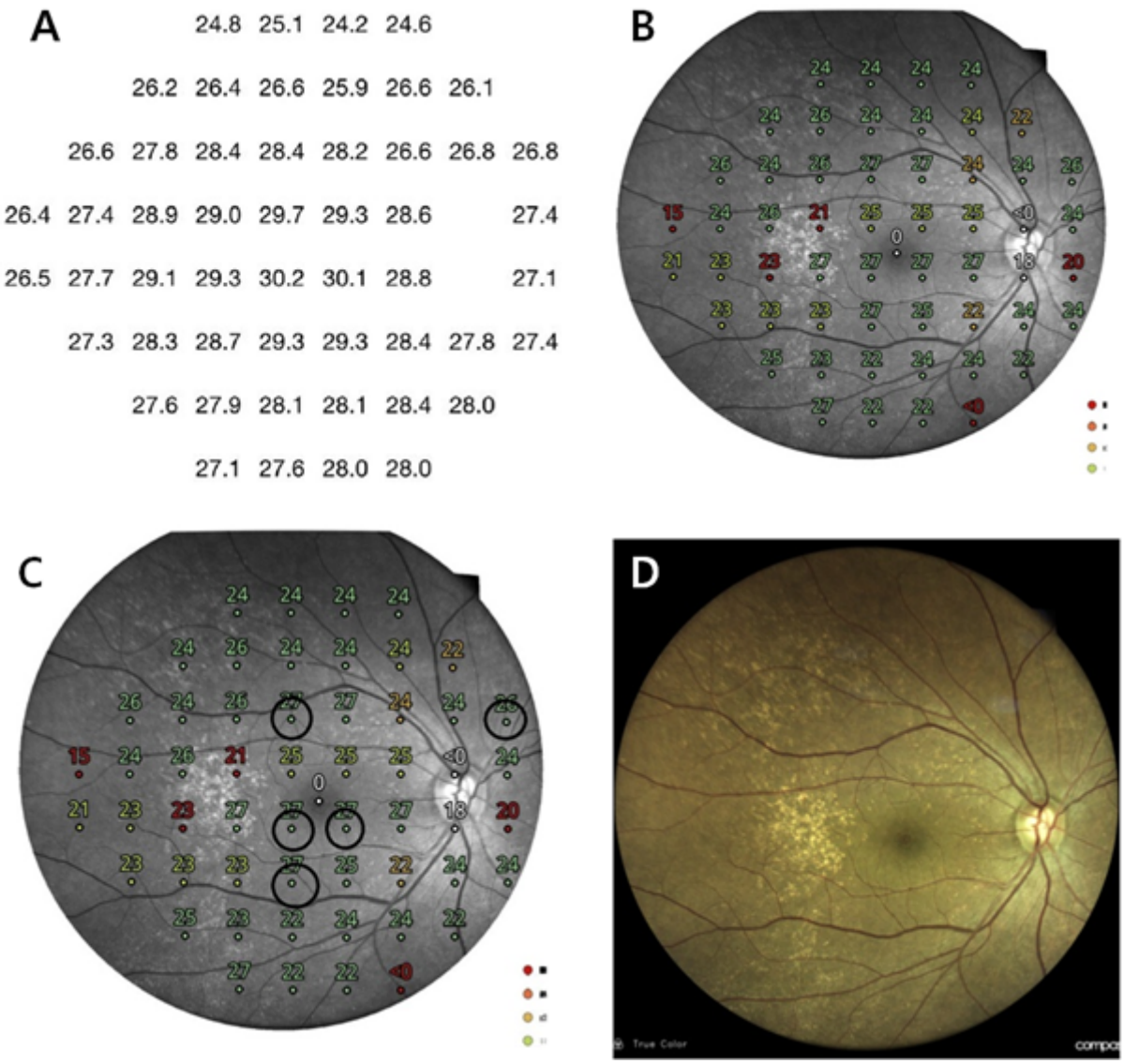

Figure 1

Average sensitivity (decibels [dB]) for each of the 52 locations considered in this analysis for Compass fundus microperimeter in the healthy subjects (A) represented and cuticular drusen patients (B). Cuticular drusen area and non-cuticular drusen area described as black circle (C), and reference photo used for discriminating drusen area and non-drusen area (D).

The average pairwise difference per location in the patients from healthy subjects was used to find out the difference significantly between cuticular drusen area and non-cuticular drusen area (all p>0.05, Mann whitney U test).

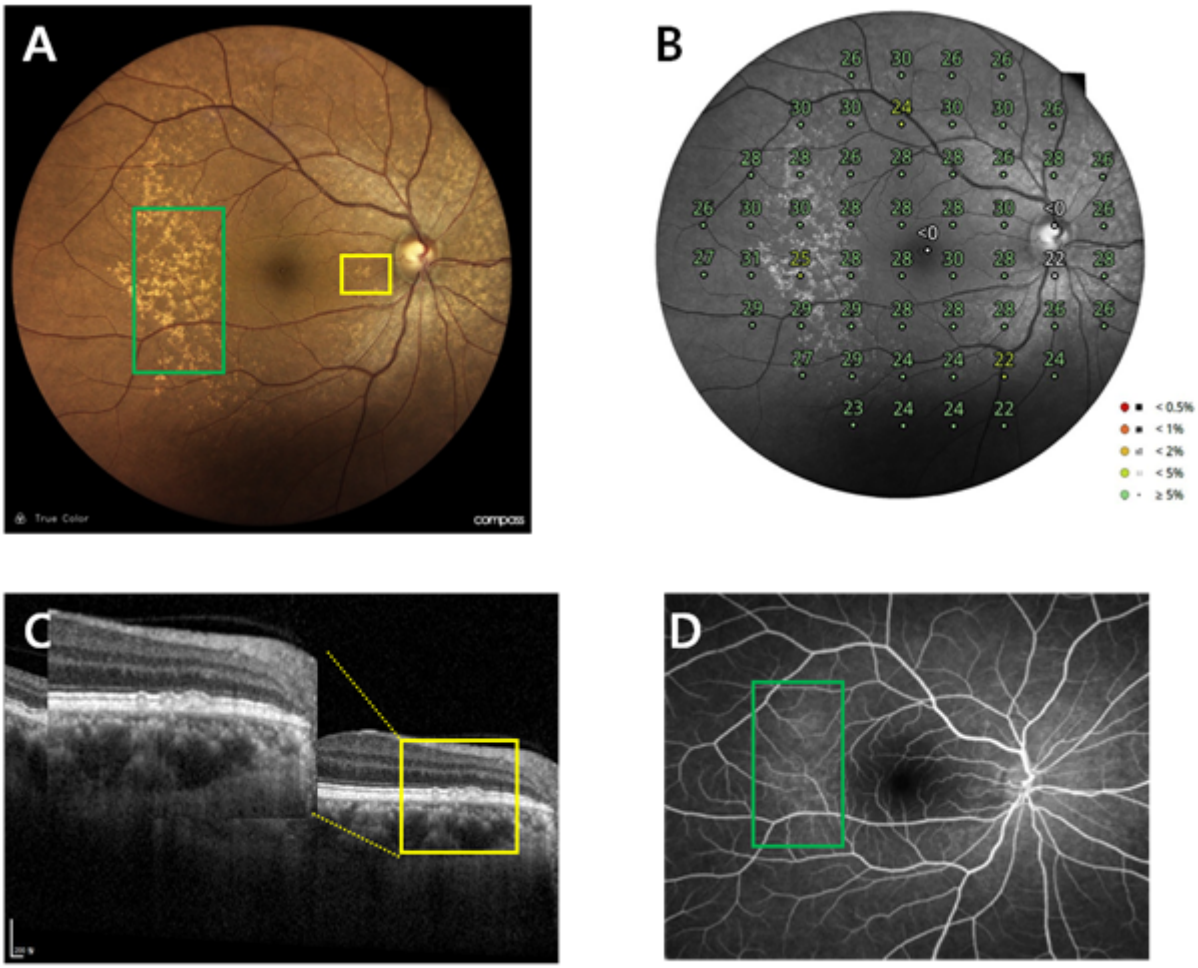

Figure 2

Representative example of Right eyes with cuticular drusen (A), microperimetry in eyes with cuticular drusen (B), shallow elevation of the retinal pigment epithelium in type 1 pattern on SD OCT (C), and hyperfluorescent in the early arteriovenous phase of fluorescein angiography (D).

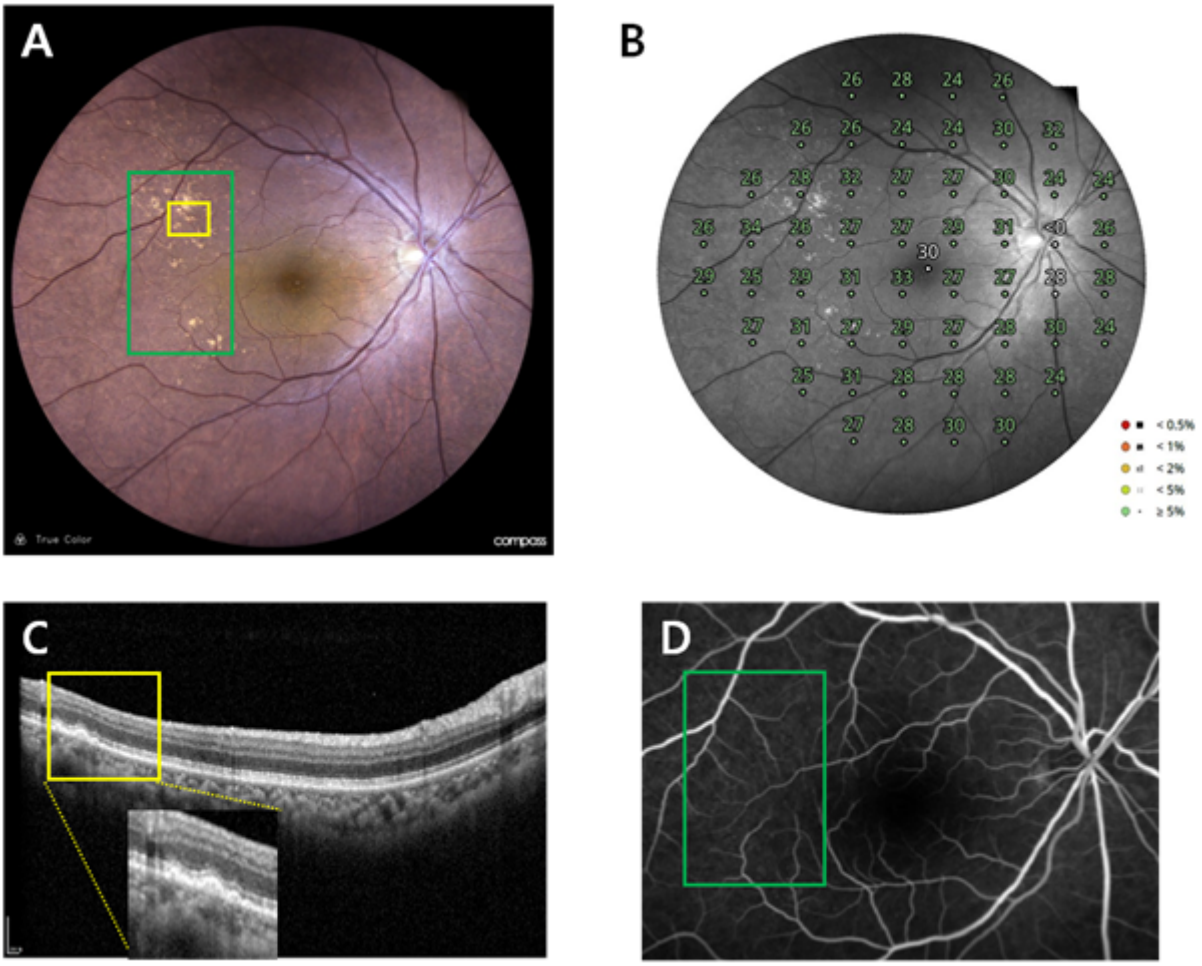

Figure 3

Representative example of Right eyes with cuticular drusen (A), microperimetry in eyes with cuticular drusen (B), sub retinal pigment epithelium triangular morphologic features, resulting in a saw-tooth appearance in type 2 pattern on SD OCT (C), and hyperfluorescent in the early arteriovenous phase of fluorescein angiography (D).

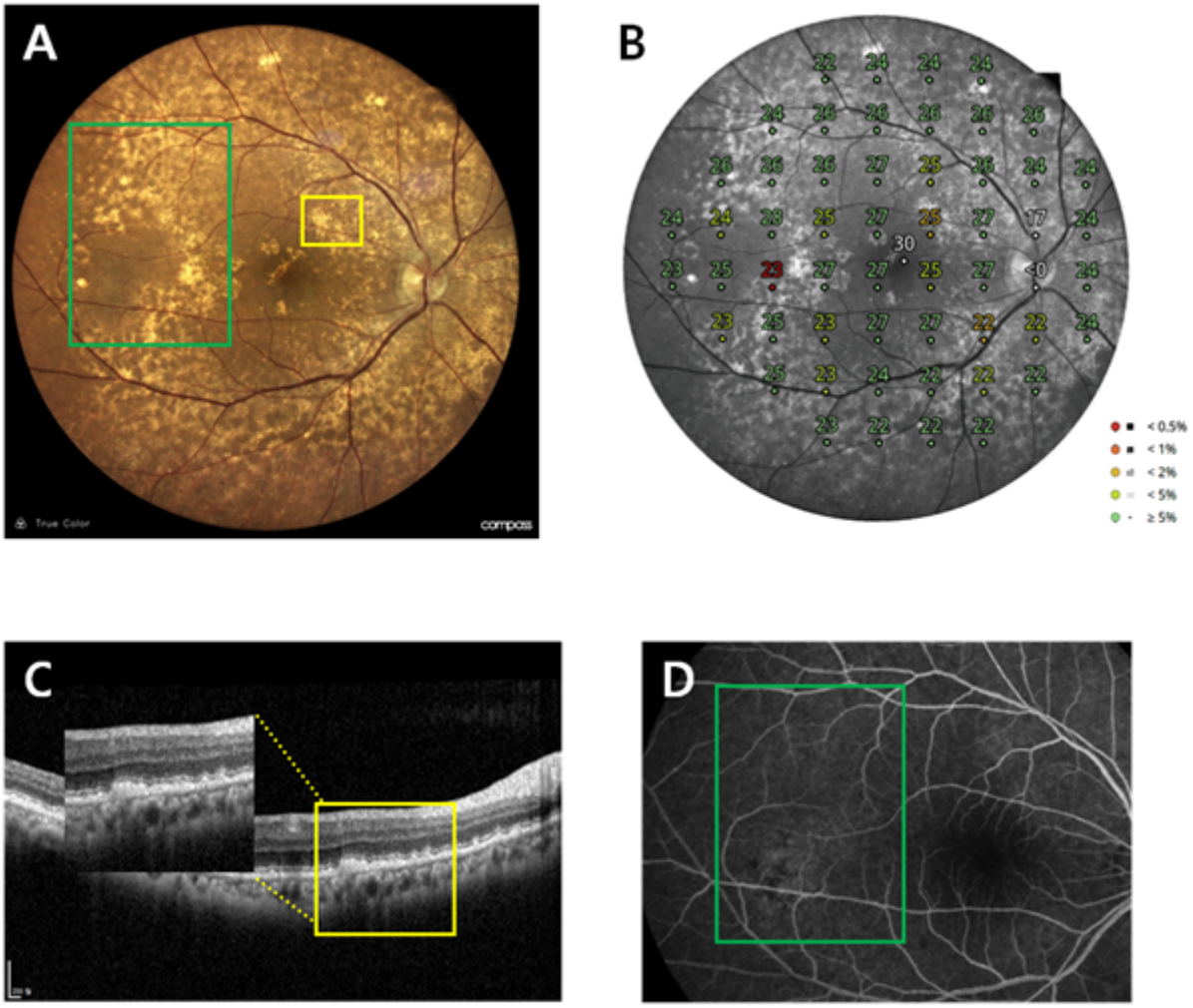

Figure 4

Representative example of Right eyes with cuticular drusen (A), microperimetry in eyes with cuticular drusen (B), broad, mound-like elevation of the RPE in type 3 pattern on SD OCT (C), and hyperfluorescent in the early arteriovenous phase of fluorescein angiography (D).