

Enhanced Depth Imaging Optical Coherence Tomography Technology Reveals a Significant Association Between Optic Nerve Drusen Anterior Displacement and Retinal Nerve Fiber Layer Thinning Over Time

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Background: Optic disc drusen (ODD) are a dynamic phenomenon, and their appearance, size, and relative location may change. The purpose of this study is to evaluate and quantify the longitudinal changes of buried ODD with enhanced depth imaging (EDI) optical coherence tomography (OCT) over time.

Methods: ODD were analyzed with Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) and EDI technology. The peripapillary retinal nerve fiber layer (RNFL) thickness was also measured. The size and depth of ODD were compared between the baseline and study visit (at least 2 years of follow-up), and the changes were correlated with mean RNFL thickness. The repeatability, coefficient of variation, and cutoff values for size and depth on EDI-OCT were calculated.

Results: Of 21 previously identified patients with ODD, only 12 patients (21 eyes) met the most recent diagnostic criteria according to the ODD Studies Consortium recommendations for using OCT-EDI technology. The 21 eyes were reanalyzed after a mean period of 44.7 ± 13.2 months (range: 24–71 months). Overall, 132 ODD were evaluated with a mean of 6.1 ± 2.5 ODD per eye and 1.9 ± 1.1 ODD per scan. Overall, we found a significant forward movement of the drusen between visits ($P = 0.01$). Most drusen (67.4%) moved anteriorly, and in approximately one-third (35.6%), this displacement exceeded the cutoff value ($64.28 \mu\text{m}$). Furthermore, we found a significant correlation between ODD shallowing and RNFL thinning during the follow-up ($P \leq 0.03$; $R \geq 0.370$). We did not find any significant changes in size measurements ($P = 0.10$) over time.

Conclusions: In approximately one-third of buried ODD, a significant anterior movement occurred over 2 years of

follow-up, and this movement was associated with significant RNFL thinning. By contrast, no significant change was detected in the size of the buried ODD.

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Optic disc drusen (ODD) are acellular deposits of calcium, amino acids, nucleic acids, and mucopolysaccharides that accumulate in front of the lamina cribrosa in the optic nerve head (1–3). The prevalence of ODD using conventional methods ranges between 0.4% and 2.4%, and ODD are more common in women and less frequent in African and Asian people (1,2,4). Using optical coherence tomography (OCT) criteria, the prevalence of drusen has been reported to be as high as 14.6% in healthy subjects (5).

When ODD are superficial or near the surface, they can be observed directly by ophthalmoscopy as yellow granular deposits and do not present diagnostic confusion (6,7). However, in many cases, ODD are not visible due to being either very small, poorly calcified or deeper, giving the appearance of optic disc elevation (pseudopapilledema), which can be confused with a papilledema caused by intracranial hypertension or other optic neuropathies, so the differential diagnosis is essential (6,7).

The development of enhanced depth imaging (EDI) OCT and its commercialization in 2008 has allowed great progress in the qualitative, quantitative, and dynamic in vivo examination of ODD (8–12), because it has a higher penetration ($500\text{--}800 \mu\text{m}$ deeper) than conventional OCT (7,9,11–14).

Recently, the Optic Disc Drusen Studies Consortium, formed by a group of neuro-ophthalmologists, developed guidelines for the diagnostic criteria for ODD using EDI-

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OCT technology (15). This consortium concluded that ODD are located above the lamina cribrosa, always have a signal-poor core, and are often seen with a hyperreflective margin. Sometimes, ODD are seen as conglomerates of smaller ODD with internal reflectivity within the signal-poor core (15). Moreover, the peripapillary hyperreflective ovoid mass-like structures (PHOMS) and hyperreflective horizontal lines should be excluded as a criterion for the diagnosis of ODD.

However, ODD are not static; they are a dynamic phenomenon, and their appearance, size, and relative location may change over time (6,7,11). However, to the best of our knowledge, there have been no studies that used EDI-OCT to evaluate the longitudinal morphological changes of buried ODD and their relationship with retinal nerve fiber layer (RNFL) changes. In addition, there is no information regarding the accuracy of the size and depth measurements of the buried ODD analyzed with EDI-OCT technology.

Therefore, the purpose of this study was to evaluate the longitudinal changes in buried ODD (size and depth) by EDI-OCT technology, and to determine the association of these changes with changes in RNFL thickness.

METHODS

Subjects

Patients with a prior diagnosis of buried ODD by EDI-OCT at the Neuro-ophthalmology unit of the Ramón y Cajal University Hospital (Madrid, Spain) and at least 2 years of follow-up were included in the study. All patients signed an informed consent form to participate in the study according to the Declaration of Helsinki. The study was conducted after the approval of the Clinical Research Ethics Committee of the same hospital.

It was required that the OCT pattern of buried ODD matched the criteria of the Optic Disc Drusen Studies Consortium (15) for inclusion in this study (Fig. 1).

Patients with bad fixation or collaboration, corneal pathology, opacity of media, or intraocular or systemic diseases that affect the optic nerve were excluded. In addition, patients in whom the image quality obtained with EDI-OCT was poor or the edges or limits of the buried ODD could not be determined were also excluded.

Measurement Method

The buried ODD and optic nerve head were analyzed with a Spectralis OCT device (Heidelberg Engineering, Heidelberg, Germany) in a dark room. The OCT device (EDI mode) was set to image a 5×15 -degree rectangle for vertical scans centered on the optic disc. This rectangle was scanned with 13 sections (interval between sections, approximately $120 \mu\text{m}$), and each section had an average of 16 OCT frames.

The “follow-up” option available on the Spectralis OCT was used, which allows the new scan to be made at the same

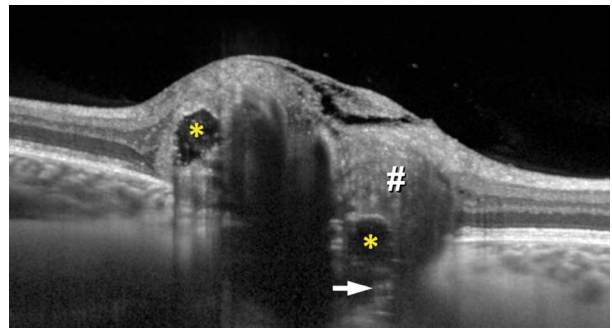


FIG. 1. ODD patterns in a single scan with EDI-OCT: 2 ODD with a typical pattern showing a signal-poor core and hyperreflective margins (*). The peripapillary hyperreflective ovoid mass-like structure (#) and the hyperreflective lines (white arrow) are not included in the ODD recommended criteria diagnosis by the ODD Studies Consortium (15). EDI, enhanced depth imaging; OCT, optical coherence tomography; ODD, optic disc drusen.

point of the optic nerve head using the en face view as the reference for the follow-up scan (Fig. 2).

In 12 eyes, a second measurement was made during the study visit, using the “follow-up” option, to analyze the repeatability of the images obtained with EDI-OCT technology. For this purpose, the patient was asked to remove their head from the device and put it back on the chinrest to perform the measurement again.

Subsequently, the EDI-OCT images of the 13 scans of each eye were exported, both from the first visit and from the last study visit. These images were processed with the ImageJ program (National Institutes of Health, MD) that allows for visualizing images and analyzing all types of dimensions, such as distances, angles, perimeters, and areas, among others. With previously calibrated images, the area (mm^2) and the linear distance (μm) to the optic nerve head surface of each buried ODD were quantified by the same observer (Fig. 3).

The RNFL thickness was also measured using the Spectralis OCT, which performed, for this purpose, a circular scan centered automatically on the papilla with a diameter of 3.4 mm and a scan speed of 40,000 A-Scan/second. The mean global and sectorial RNFL thicknesses were registered.

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, IL) statistical package for Windows. The normality of the data was assessed using the Kolmogorov–Smirnov test. The significance level was set at 5%. A descriptive analysis of the buried ODD sample was performed by calculating the frequencies for the categorical variables and the mean and SD for continuous variables (age, years of evolution, size, and depth of the buried ODD).

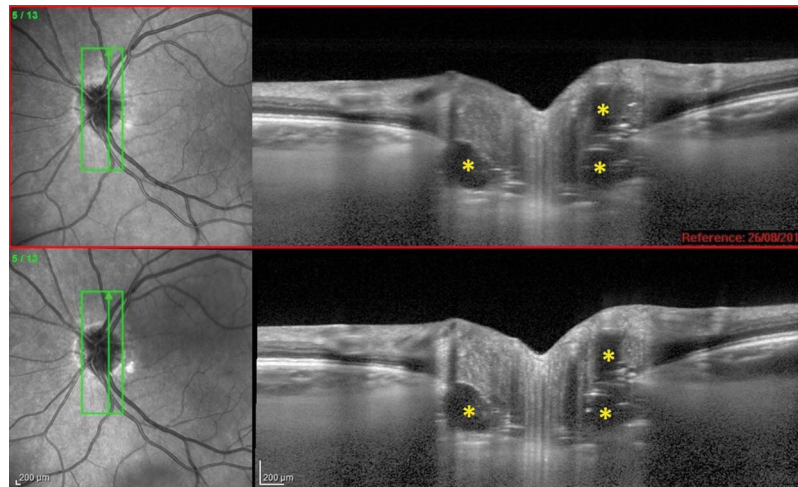


FIG. 2. Image captured with EDI mode with Spectralis OCT (13 vertical scans) shows the optic nerve head in which 3 ODD with a typical pattern can be visualized. Top: image captured at the baseline visit; below: image captured during the study visit with the “follow-up” function scan. EDI, enhanced depth imaging; OCT, optical coherence tomography; ODD, optic disc drusen.

Thirteen vertical scans per eye were obtained with EDI-OCT technology. Each scan was analyzed separately in terms of the number, size, and depth of the drusen to study the possible longitudinal changes.

Student *t* test was used to compare the size and depth of the buried ODD between the baseline and study visit ($P \leq 0.05$ was statistically significant). Pearson correlation coefficient was used to assess the association between RNFL thickness and the size and relative position of the ODD ($P \leq 0.05$ was statistically significant).

The repeatability of the measurements was calculated to determine the variability of the EDI-OCT technology. The coefficient of variation (CV); percentage value of the measurement's variation defined as the ratio of Sw to the overall mean ($CV = Sw/\text{mean} \times 100$ [%]) (16); and the intraclass correlation coefficient (ICC; classified as follows: less than 0.75 = poor agreement; 0.75 to less than 0.90 = moderate agreement; 0.90 or greater = high agreement) (17) were calculated. Moreover, the differences between the consecutive measurements of buried ODD were plotted against the means of both measurements, and 95% limits of agreement (LoA) were calculated (mean difference ± 1.96 SD) (18).

The upper limit of the 95% confidence interval of the 95% LoA was considered the cutoff value that indicated a possible temporary change in size and relative position of the buried ODD when 2 measurements were made in the follow-up of these patients.

RESULTS

Demographic Data

Twenty-one patients with a prior diagnosis of buried ODD by EDI-OCT and a follow-up of at least 2 years were re-evaluated with the same EDI-OCT device. Of these 21

patients, 9 (mean age: 14.6 ± 9.3 years) had a nonspecific pattern of buried ODD according to The Optic Disc Drusen Studies Consortium (PHOMS “peripapillary hyperreflective ovoid mass-like structures” and/or hyperreflective lines) (15), so only 12 patients were finally included in the study. Eight patients were women and 4 were men.

Nine patients presented bilateral buried ODD, and 3 patients presented unilateral buried ODD, so a total of 21 eyes were analyzed. Fourteen eyes of 8 patients had only buried drusen, and 7 eyes of 4 patients had both visible and buried drusen identified by EDI. Longitudinal changes were analyzed just in buried drusen with the EDI pattern above mentioned (a signal-poor core and hyperreflective margins).

Overall, the mean age was 40.3 ± 18.3 years.

The mean time lapsed from the baseline diagnostic visit to the follow-up visit of this study was 44.7 ± 13.2 months (range 24–71 months).

Cutoff Values of Changes in Depth and Size

Two consecutive image captures were performed in 7 patients (12 eyes) with 70 buried ODD to calculate the repeatability of depth and size measurements and to determine the cutoff value for assessing the significance of changes in depth or size. The cutoff values were $64.28 \mu\text{m}$ for depth and 0.065 mm^2 for size. Changes detected in follow-up that exceeded those values were considered significant (Table 1).

Longitudinal Changes in Depth and Size

A total of 132 buried ODD were identified and measured in the 21 eyes, with a mean of 6.1 ± 2.5 ODD per eye (range 1–10) and 1.9 ± 1.1 ODD per scan (range 1–7).

Overall, 89 buried ODD (67.4%) moved anteriorly, 39 (29.6%) deepened, and 4 (3%) remained unchanged over

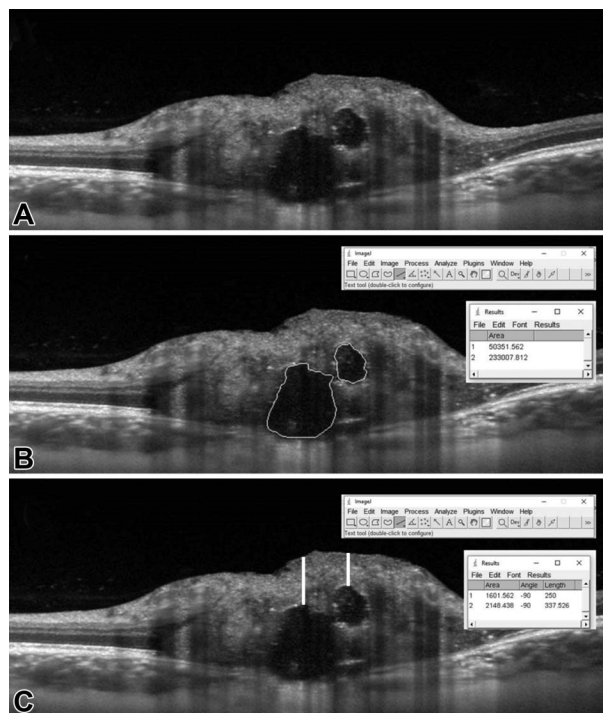


FIG. 3. Example of measurement of the size and depth of ODD with the ImageJ program. **A.** Image exported from the OCT Spectralis equipment and used to perform the measurement with the ImageJ program. **B.** Example of the area measurements (the white line delimits the edge of the ODD: 0.050 and 0.233 mm², respectively). **(C).** Example of the ODD depth measurements with respect to the surface, between the top of the ODD and the surface of the optic disc: 250 and 337.5 µm, respectively. OCT, optical coherence tomography; ODD, optic disc drusen.

time. A significant buried ODD shallowing from baseline to follow-up was found ($P = 0.01$).

In the group of 89 buried ODD showing a forward displacement, the mean movement was 49.2 ± 48.7 µm (ranging from 4 to 262 µm). In 36 of them (40.5%), belonging to 13 eyes of 9 patients, the shallowing was larger than the cutoff value (64.28 µm) ($P < 0.01$) (35.6% of the total buried ODD sample) (Fig. 4). The mean age of these patients was 29.8 ± 11.5 years, about 24 years younger than patients with buried ODD having no significant displacement (54 ± 6.2 years) ($P < 0.01$).

Overall, 61 buried drusen (46.2%) decreased in size with respect to the baseline visit, and 71 (53.8%) enlarged. No

significant changes were observed in the buried ODD area over time ($P = 0.10$) (Table 2). An enlargement greater than the cutoff value (0.065 mm²) was observed in only 9 buried ODD (6.8%).

Relationship Between Buried Optic Disc Drusen and Retinal Nerve Fiber Layer Thickness

Regarding the relationship between the size of the buried ODD and the RNFL thickness, a statistically significant inverse correlation was found at baseline in all sectors ($P \leq 0.05$; $R \geq -0.261$) and in the temporal-inferior ($P = 0.02$; $R = -0.152$) and temporal-superior ($P = 0.03$; $R = -0.204$) sectors in the study visit.

A significant correlation was found between the depth of buried ODD and the peripapillary RNFL thickness in all sectors, so that the deeper the drusen, the greater the RNFL thickness at both the baseline ($P \leq 0.04$; $R \leq 0.233$) and at follow-up study ($P \leq 0.01$; $R \leq 0.379$) visits.

The mean differences in RNFL thickness detected at the follow-up visit are shown in Table 3. RNFL thinning was found in all sectors, although it was only significant for the average and the nasal-inferior sector ($P < 0.05$) (Table 3).

Because the distance taken from the RNFL to the ODD can be influenced by the progressive RNFL thinning, we also measured the distance from a reference line connecting the opposite borders of the Bruch membrane opening (BMO) to the buried ODD (Fig. 4). This distance significantly increased from 84.3 ± 316.3 µm at baseline visit to 116.53 ± 321.16 µm at the last study visit ($P < 0.01$).

DISCUSSION

EDI-OCT technology has been widely studied in recent years to assess ODD size, position, and location (8,9,15,19–21). Nevertheless, to the best of our knowledge, there is no information regarding the morphological changes of buried ODD over time using EDI-OCT technology.

ODD can change over time, as evidenced by the change from deep buried drusen typical of childhood to the visible superficial drusen seen in adults (6,21–24). Moreover, it has been reported that these changes mainly occur during the teenage years (23,25). Malmqvist et al (25) reported changes in optic disc appearance after a median follow-up of 5.6 years in 8 patients with ODD and noted that the ODD assumed a more superficial location during early adulthood. Hoover et al (26) reported that the mean age

TABLE 1. Repeatability of the optic disc drusen depth and size measurements obtained with enhanced depth imaging-optical coherence tomography technology

	Mean Difference $\pm$ SD	LoA 95%	95% CI Upper Limit LoA 95%	CV%	ICC
Depth, µm	1.951 ± 27.20	–51.35 to 55.26	64.28	6.21%	0.892
Size, mm ²	-0.010 ± 0.033	–0.074 to 0.055	0.065	14.57%	0.869

CI, confidence interval; CV, coefficient of variation; ICC, intraclass correlation coefficient; LoA, limits of agreement.

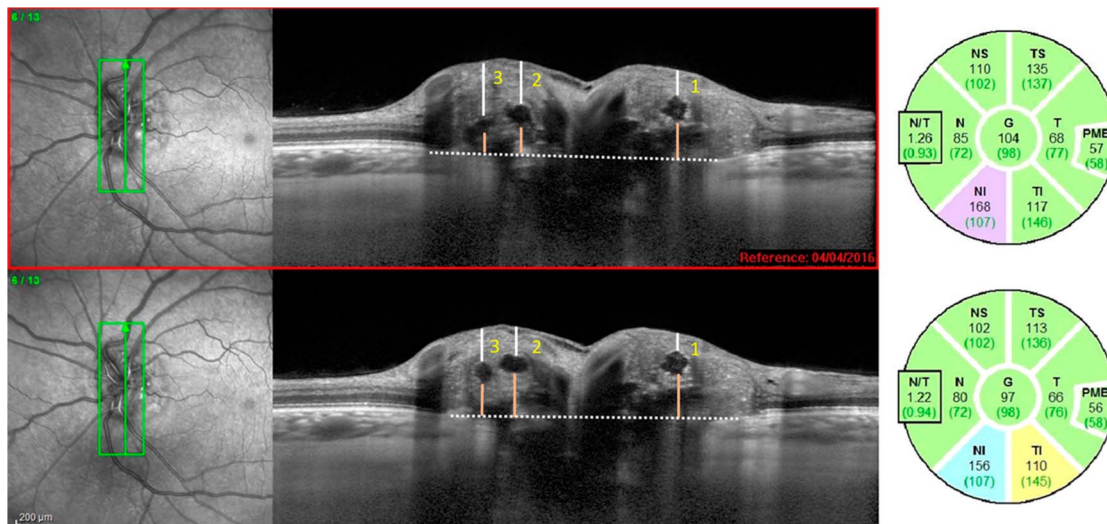


FIG. 4. EDI-OCT scan of a 26-year-old woman at the initial visit (top) and 3 years later (bottom) showing that 3 buried ODD, numbered as 1, 2, and 3, moved anteriorly. Distances to the surface of the optic disc (white lines) and to the Bruch membrane opening (BMO) (orange lines) decreased and increased, respectively, supporting the forward movement of the 3 drusen. Depth differences to the surface of the optic disc between visits were higher than the cutoff value in the 3 ODD: 74.9 μm (1), 120.9 μm (2), and 187.5 μm (3). The distance between ODD and BMO (discontinuous white line) increased with respect to initial visit in the 3 drusen: 30.3 μm (1), 94.2 μm (2), and 60.6 μm (3). A thinning of the retinal nerve fiber layer thickness over time is shown in the right column. EDI, enhanced depth imaging; OCT, optical coherence tomography; ODD, optic disc drusen.

at which drusen became superficial and visible was 12.1 years.

In the current study, in line with previous studies, we found a significant shallowing of buried ODD over time ($P < 0.01$). Overall, a forward movement was observed in 67.4% of the buried ODD. It has been reported that there might be inaccuracy in the EDI-OCT despite using the follow-up function, leading to a slightly different location of the follow-up scan that results in a false interpretation of progression (27). Due to the measurement variability of the Spectralis EDI-OCT, only buried ODD depth changes greater than 64.28 μm were considered as a real longitudinal change. According to this cutoff value, a significant forward displacement was observed in 35.6% of the total buried ODD sample. This significant movement occurred in 9 patients (13 eyes) who were significantly younger than

patients with no significant buried ODD displacement (29.8 vs 54 years, $P < 0.01$).

In addition, we found that peripapillary RNFL thickness was significantly related to this progressive shallowing. Noval et al (28) also found that eyes with superficial ODD exhibited RNFL thinning in comparison with healthy control eyes. Similarly, Malmqvist et al (29) reported a significant correlation between the depth of the ODD and the peripapillary RNFL thickness.

In light of these results, one may argue that the distance measured from the RNFL to the buried ODD is influenced by the measurements of the RNFL thickness. To avoid the possible relationship with the RNFL thickness, we measured the distance from the BMO to the inferior part of the ODD, not only the linear distance to the optic nerve head surface (Fig. 4). This distance significantly increased by a

TABLE 2. Mean value of the size and position of the optic disc drusen at the baseline visit and at the study visit in the total sample and in groups with changes greater than the cutoff values

	ODD Sample	Baseline Visit Mean $\pm$ SD (Max–Min)	Study Visit Mean $\pm$ SD (Max–Min)	P^*	Mean Difference $\pm$ SD
Depth, μm	Total (n = 132)	390.7 $\pm$ 175.6 (87–950)	367.4 $\pm$ 162.4 (65–850)	0.01	–23.2 $\pm$ 59.4
	Shallowing $\geq$ cutoff value (n = 36)	496.6 $\pm$ 171.9 (141–950)	377.9 $\pm$ 161.4 (66–779)	<0.01	–118.6 $\pm$ 63.8
Size, mm^2	Total (n = 132)	0.123 $\pm$ 0.133 (0.002–0.634)	0.128 $\pm$ 0.135 (0.002–0.681)	0.10	0.005 $\pm$ 0.04

Bold values indicates a statistically significant difference with a P-value less than 0.05.

*Student paired t test ($P \leq 0.05$ statistically significant).

TABLE 3. Mean value of the retinal nerve fiber layer thickness in all sectors in the baseline visit and at the study visit in the total sample (n = 132 eyes) and in optic disc drusen showing shallowing with larger changes than the cutoff value (64.28 μ m) (n = 36 eyes)

Retinal Nerve Fiber Layer Thickness Region	Optic Disc Drusen Sample	Baseline Visit Mean $\pm$ SD (Max–Min)	Study Visit Mean $\pm$ SD (Max–Min)	Mean P* Difference $\pm$ SD
Average	Total	94.5 $\pm$ 65.1 (37–268)	82.2 $\pm$ 45.3 (36–199)	0.02 12.3 $\pm$ 21.6
	Shallowing > cutoff	102.8 $\pm$ 77.6 (37–268)	87.7 $\pm$ 54.3 (36–199)	0.03 15.1 $\pm$ 24.4
Nasal-superior	Total	94.9 $\pm$ 81.7 (30–333)	82.2 $\pm$ 63.0 (30–251)	0.06 12.8 $\pm$ 27.9
	Shallowing > cutoff	100.9 $\pm$ 93.1 (30–333)	88.3 $\pm$ 75.1 (30–251)	0.15 12.6 $\pm$ 28.3
Nasal	Total	65.1 $\pm$ 49.2 (23–206)	57.5 $\pm$ 36.6 (22–147)	0.17 7.7 $\pm$ 24.5
	Shallowing > cutoff	62.4 $\pm$ 41.5 (23–150)	59.3 $\pm$ 40.7 (22–147)	0.38 3.1 $\pm$ 11.8
Nasal-inferior	Total	122.3 $\pm$ 89.7 (24–352)	108.6 $\pm$ 65.6 (24–258)	0.03 13.7 $\pm$ 26.7
	Shallowing > cutoff	134.0 $\pm$ 106.5 (24–352)	114.0 $\pm$ 75.9 (24–258)	0.04 20.0 $\pm$ 32.7
Temporal-inferior	Total	127.8 $\pm$ 96.5 (30–412)	108.4 $\pm$ 57.8 (28–245)	0.08 19.5 $\pm$ 46.7
	Shallowing > cutoff	143.3 $\pm$ 120.4 (30–412)	110.0 $\pm$ 68.8 (28–245)	0.07 33.3 $\pm$ 56.8
Temporal	Total	86.2 $\pm$ 79.5 (33–345)	74.0 $\pm$ 45.7 (35–211)	0.15 12.2 $\pm$ 36.5
	Shallowing > cutoff	102.9 $\pm$ 99.9 (35–345)	83.3 $\pm$ 56.8 (35–211)	0.17 19.7 $\pm$ 46.3
Temporal-superior	Total	107.4 $\pm$ 61.5 (37–268)	95.4 $\pm$ 62.8 (39–307)	0.14 12.0 $\pm$ 34.9
	Shallowing > cutoff	112.8 $\pm$ 71.8 (38–248)	102.9 $\pm$ 77.1 (39–307)	0.42 9.8 $\pm$ 40.6

Bold values indicates a statistically significant difference with a P-value less than 0.05.

*Student paired t test ($P \leq 0.05$ statistically significant).

mean of 30 μ m from baseline visit to the study visit ($P < 0.01$), further supporting the fact that buried ODD moves anteriorly over time. Although measuring the distance from the lamina cribrosa (LC) to the ODD could be even more convincing, it was not possible because the drusen do not allow clearly to delineate the anterior border of LC in most cases.

In contrast to depth, in our study, we did not find any significant differences in buried ODD size during at least 2 years of follow-up. This finding may be because most patients included in this study were adults. We found a significant inverse correlation between the buried ODD area and RNFL thickness, which means that the larger the buried ODD size was, the lower the RNFL thickness was. In line with our results, Sato et al (10) observed a significant inverse correlation between the diameter of the ODD and the average RNFL thickness.

ODD are 3-dimensional structures with a highly irregular shape. However, we have captured EDI images only in the vertical plane, and the bidimensional analysis of the ODD has been done by studying only the size and relative position. Despite this limitation, in the current study, we demonstrated a significant forward displacement of buried ODD over 2 years of follow-up, and this forward displacement was associated with significant RNFL thinning. By contrast, no significant change was detected in the size of the buried drusen. Further studies are needed in the

future to analyze ODD in a 3-dimensional way with vertical, horizontal, and en face scans to assess the position and shape of the buried ODD and to better determine the longitudinal changes.

STATEMENT OF AUTHORSHIP

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