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Early detection of tamoxifen-induced retinal injury: ellipsoid zone reflectivity as a sensitive structural marker

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Abstract

Purpose To investigate early structural alterations in the outer retina and choroid of tamoxifen-treated patients without clinically detectable retinopathy by quantitatively assessing reflectivity changes of the external limiting membrane (ELM), ellipsoid zone (EZ), and retinal pigment epithelium (RPE), along with the choroidal vascularity index (CVI).

Methods The study included 45 eyes of 45 tamoxifen-treated women and 50 eyes of 50 age- and sex-matched healthy female controls. ELM, EZ, and RPE reflectivity was measured along foveal, parafoveal, and perifoveal axes. CVI was derived using a standardized binarization method. Correlations between reflectivity metrics and tamoxifen exposure indices were analyzed.

Results Tamoxifen users showed a marked reduction in EZ reflectivity at the central fovea and at the temporal perifovea ($p=0.005$ and $p=0.037$, respectively), accompanied by a corresponding decrease in relative EZ values at the central fovea and at the temporal parafovea ($p=0.012$ and $p=0.039$, respectively). In contrast, ELM and RPE reflectivity metrics remained stable across all evaluated regions ($p>0.05$). CVI measurements revealed no significant differences between the patient and control groups ($p>0.05$). Within the tamoxifen cohort, treatment duration demonstrated weak but significant positive associations with central foveal ELM reflectivity ($r=0.389$, $p=0.008$), whereas age was negatively correlated with EZ reflectivity in the nasal parafoveal region ($r=-0.331$, $p=0.026$).

Conclusions Early tamoxifen exposure appears to affect the EZ before detectable alterations become evident in the ELM, RPE, or choroid. These findings suggest that subtle EZ disruption may represent an early structural indicator of tamoxifen-related retinal involvement and could potentially aid in identifying patients who may require closer monitoring. However, longitudinal studies are needed to confirm these findings and clarify their clinical significance.

Keywords Choroidal vascularity index, Ellipsoid zone, External limiting membrane, Outer retinal reflectivity, Swept-source OCT, Tamoxifen retinopathy

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Introduction

Tamoxifen is a nonsteroidal selective estrogen-receptor antagonist that inhibits estrogen binding and is commonly used to treat hormone receptor–positive breast cancer [1]. Tamoxifen is associated with systemic adverse events such as night sweats, hot flashes, vaginal dryness, and venous thromboembolic disease, yet there has been a growing focus on the ocular toxicity of tamoxifen [2]. In the literature, tamoxifen-related ocular toxicity has been reported from the cornea and lens to the retina, retinal pigment epithelium (RPE), and optic nerve, with retinopathy being the most frequently described adverse effect [3, 4]. Common retinal findings include crystalline intraretinal deposits, cystoid macular edema, foveal cavitation, and macular telangiectasia. Retinopathy is typically identified once fundus abnormalities are apparent or when visual function is compromised. However, its underlying mechanisms of retinopathy are not completely understood, mostly due to the challenge of precisely identifying early-stage alterations [5].

To determine the optimal timing and duration of ocular surveillance in patients receiving tamoxifen, it is essential to understand the underlying mechanisms of retinopathy, and several pathways have been proposed to explain tamoxifen-associated retinal toxicity. Cho et al. [6] established that tamoxifen promotes oxidative stress in RPE and photoreceptor cells, leading to cellular damage and the activation of autophagy. Tamoxifen may also cause Müller cell dysfunction and glutamate-mediated neuronal damage by blocking glutamate-aspartate transporters, perhaps leading to foveal cavitations and subsequent disruption of the external limiting membrane (ELM) [7]. In their optical coherence tomography (OCT)-based study, Bolukbasi et al. [8] revealed a markedly elevated choroidal thickness among tamoxifen users relative to healthy controls. Notably, several reports have suggested that early retinal changes may be reversible following discontinuation of tamoxifen therapy [9]. Thus, recognizing early changes in the ELM, EZ, and RPE layers, along with associated choroidal involvement, may improve clinical outcomes in the management of tamoxifen-associated ocular toxicity. Because of this need for early detection, OCT has become the primary imaging modality for identifying early retinal alterations in tamoxifen toxicity [8]. Beyond qualitative assessment, OCT-based reflectivity analysis offers a quantitative way to evaluate the integrity of specific retinal layers. Gin et al. [10], for example, demonstrated reduced EZ reflectivity in intermediate age-related macular degeneration (AMD), while other studies have investigated ELM and RPE reflectance and the choroidal vascularity index (CVI) as sensitive biomarkers for drug-related retinal injury, including hydroxychloroquine [11, 12]. CVI, calculated as the ratio of luminal choroidal area (LCA) to total choroidal area (TCA) through image binarization, has also been recognized as a robust marker of choroidal vascular alterations across retinal diseases, often decreasing in affected eyes [13, 14]. In this context, the purpose of this study is to evaluate early outer retinal changes in tamoxifen users by quantitatively analyzing reflectivity modifications prior to the emergence of significant fundus abnormalities or specific OCT findings documented in existing literature. Furthermore, we aim to examine subfoveal choroidal vascular and luminal alterations as possible early indications of tamoxifen-related retinal involvement.

Materials and methods

Patient selection

This prospective observational study with a cross-sectional imaging analysis was conducted at Izmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital in accordance with ethical standards and the principles of the Declaration of Helsinki. The Clinical Research Ethics Committee of Izmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital approved the study protocol (decision number 2025/466, date: 02.06.2025). Comprehensive information about the study procedures was provided to all participants, and written informed consent was obtained from all participants.

This study included the left eyes of 45 tamoxifen-treated patients and 50 healthy female controls with comparable age distribution. Only one eye per participant was included in the analysis to avoid potential statistical bias related to inter-eye correlation and to ensure a standardized and unbiased sampling approach. Individuals with a history of retinal disease, uveitis, optic nerve disorders, glaucoma, systemic illnesses that could interfere with retinal structure, refractive errors with a spherical equivalent greater than ± 3.00 diopters, or the use of systemic drugs known to influence retinal morphology within the preceding three months including hydroxychloroquine, chloroquine, systemic or intravitreal corticosteroids, MEK inhibitors, amiodarone, retinoids, anti-VEGF agents, or other medications reported to affect retinal structure were excluded. Patients with prior ocular surgery or media opacities causing inadequate OCT image quality, as well as those with a body mass index (BMI) below 20 or above 30, were also not included to minimize the potential confounding effects of underweight and obesity on retinal and choroidal structural measurements. Inclusion criteria comprised patients receiving ongoing tamoxifen therapy for a total duration of at least one year. All patients received tamoxifen at a dosage of 20 mg per day. A thorough ophthalmologic examination and OCT assessment revealed no prominent structural lesions suggestive of tamoxifen-related ocular toxicity in any individual.

The gathered data encompassed demographic and clinical factors, including age, sex, and the presence of ocular and systemic diseases. Details related to tamoxifen administration, such as length of exposure, and daily dosing were collected.

Ophthalmic examination

All participants underwent a comprehensive ocular examination, which included the measurement of best-corrected visual acuity (BCVA) utilizing the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, slit-lamp biomicroscopy, Goldmann applanation tonometry, and dilated funduscopy. Swept-source optical coherence tomography (SS-OCT) imaging was conducted to evaluate retinal and choroidal architecture.

SS-OCT imaging was performed using the DRI OCT Triton device (Topcon, Tokyo, Japan). This device obtained images using the 9-mm radial scan protocol, which consists of 12 radial B-scan lines centered on the fovea, each composed of 1024 A-scans. Only the single horizontal scan was exported as JPG image for further analysis.

Two masked, experienced, and independent ophthalmologists (BHU and SK) performed blinded reflectivity measurements and CVI calculations on the OCT images. The mean of their independent measurements was used in the analysis to minimize inter-observer variability.

CVI calculation

The CVI was quantified using Image J software (version 1.8.0_77, Bethesda, MD, USA http://imagej.nih.gov/ij/). A line intersecting the foveal center was established with the line tool, from which 750 µm segments were delineated toward both the nasal and temporal sides, producing a total extent of 1500 µm. The TCA was outlined using the polygonal tool [15]. The choroidal region was delineated with the upper boundary defined by the RPE and the lower boundary corresponding to the bright line at the choroid-scleral junction. This region was subsequently added to the region of interest (ROI) manager. After changing photos to the 8-bit form, Niblack's autolocal threshold method was used for binarization of grayscale images [16]. After binarization, the image was converted back into an RGB format. Using the Threshold tool, the luminal region was delineated, and both luminal and stromal choroidal areas were quantified automatically based on pixel-intensity distribution. The CVI was subsequently calculated by dividing the LCA by the TCA. Figure 1 illustrates the binarization process and the subsequent calculation of CVI by dividing the LCA by the TCA.

Assessment of ELM, EZ, and RPE reflectance

The Plot Profile feature of ImageJ software was employed to determine the light reflectance of the ELM, EZ, and RPE layers. A vertical line passing through the foveal center was drawn from the vitreous interface toward the choroid to extract a unified reflectivity plot of the retinal layers. The most hyperreflective band among the outer retinal layers was recognized as the RPE, as previously described in the literature [17]. The hyperreflective layer situated above the RPE was identified as the EZ, whilst the hyperreflective band positioned above the EZ was designated as the ELM. Figure 2 illustrates the identification of the ELM, EZ, and RPE bands on the retinal reflectivity profile.

A 750-µm horizontal line was drawn extending into the nasal and temporal perifoveal regions, followed by another line positioned 1500 µm away to evaluate the parafoveal regions, with corresponding reflectivity measurements collected. The relative reflectivity of the ELM and EZ was computed in relation to the RPE. The reflectivity values of the ELM and EZ were divided by the corresponding RPE reflectivity to obtain this ratio [18].

Statistical analysis

The power analysis was conducted using G*Power software (version 3.1.9.7). Assuming a large effect size of 0.80, a significance level of 0.05, and a statistical power of 90%, the minimum required sample size was calculated as 42 participants per group. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Descriptive statistics were presented as mean ± standard deviation together with minimum and maximum values.

Group comparisons between the tamoxifen and control eyes were conducted using the independent samples t-test for normally distributed variables. Absolute and relative reflectivity measurements of the EZ, ELM, and RPE were compared separately for each retinal subregion (central fovea, nasal/temporal parafovea, and nasal/temporal perifovea), and results were summarized in tables.

Interobserver reliability for CVI and all reflectivity measurements obtained independently by two masked graders were evaluated using a two-way random effects intraclass correlation coefficient (ICC, absolute agreement). ICC values were calculated for each retinal quadrant and layer, and high inter-rater agreement was confirmed prior to further analysis.

To investigate the influence of clinical exposure factors, Pearson's correlation coefficients were used for normally distributed variables and Spearman's rho for non-normally distributed variables. Correlation analyses explored the relationships between treatment duration,

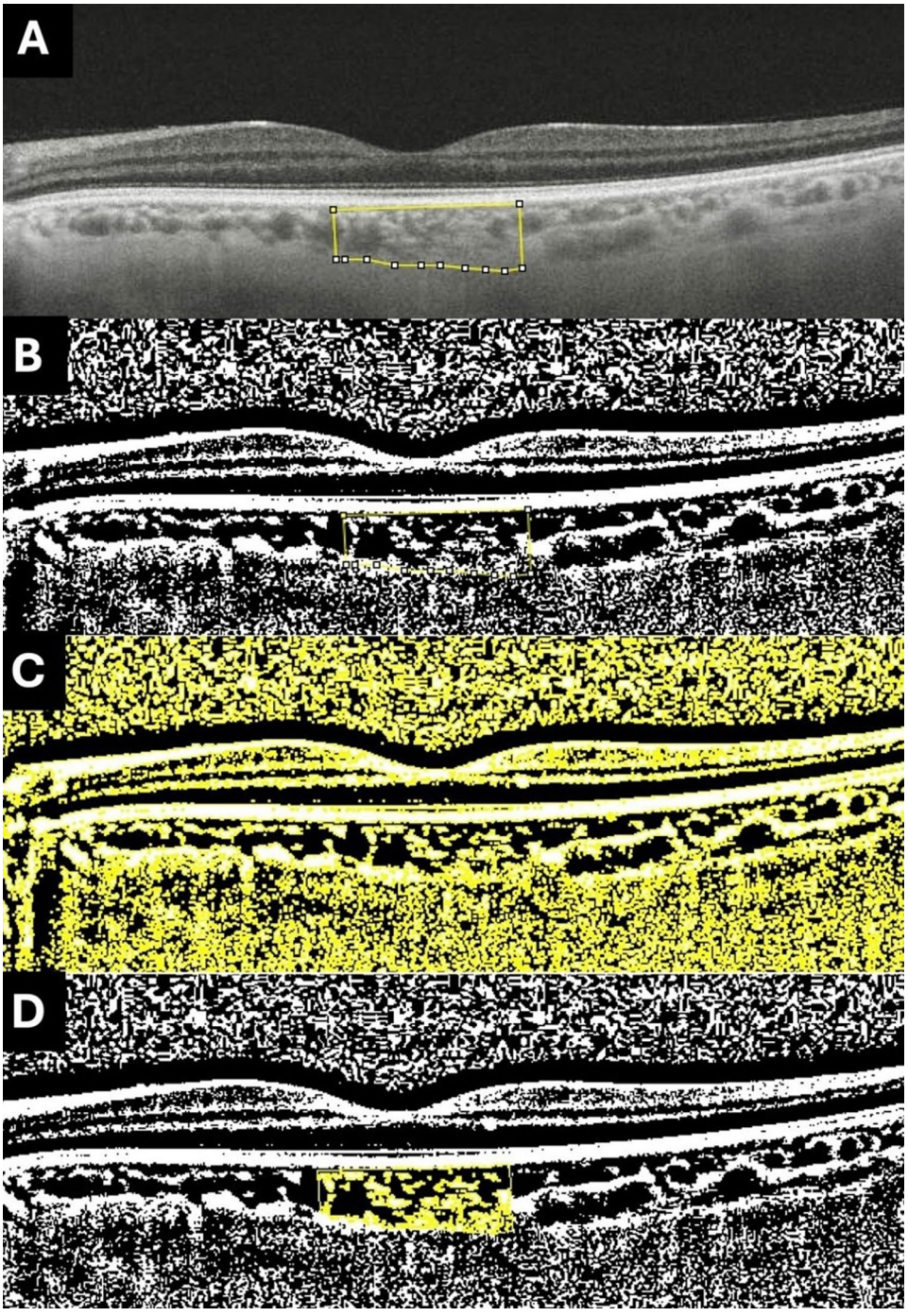

Fig. 1 Representative workflow for choroidal vascularity index (CVI) measurement using ImageJ. (**A**) Swept-source optical coherence tomography (SS-OCT) image demonstrating manual selection of the subfoveal choroidal region of interest (ROI). A 1500-µm-wide area, centered on the fovea (750 µm nasal and 750 µm temporal), extending from the retinal pigment epithelium to the choroid–sclera junction, was delineated using the ROI Manager. (**B**) The selected ROI was converted to an 8-bit image and binarized using the Niblack Auto Local Threshold method. (**C**) Color threshold adjustment was subsequently applied after RGB conversion to isolate the luminal component within the choroid. (**D**) The binarized and thresholded images were combined using the AND operation in the ROI Manager to obtain the luminal choroidal area. Total choroidal area (TCA) and luminal choroidal area (LCA) were measured automatically, and the CVI was calculated as the ratio of LCA to TCA

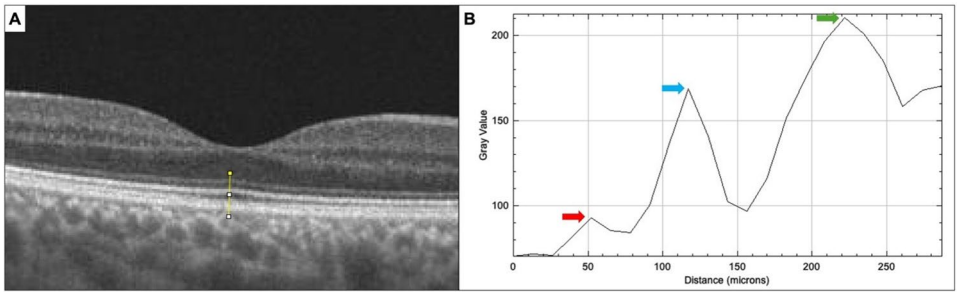

Fig. 2 Demonstration of outer retinal reflectivity measurements. (**A**) A vertical sampling line is placed on a transfoveal B-scan optical coherence tomography image using ImageJ software. (**B**) The corresponding gray-value plot shows three distinct reflectivity peaks along the sampling line, corresponding to the external limiting membrane (red arrow), the ellipsoid zone (blue arrow), and the retinal pigment epithelium (green arrow)

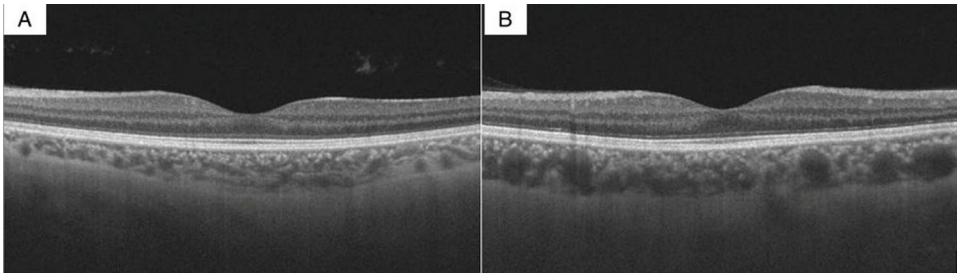

Fig. 3 Representative swept-source OCT B-scan images from a tamoxifen-treated patient and a healthy control. (**A**) Horizontal transfoveal OCT B-scan from a tamoxifen-treated patient. (**B**) Corresponding OCT B-scan from an age-matched healthy control

patient age, and absolute or relative reflectivity values in all retinal subregions, as well as CVI measurements. A p-value < 0.05 was considered statistically significant in all analyses.

Results

Demographic and clinical characteristics

A total of 45 eyes of 45 female patients receiving tamoxifen and 50 eyes of 50 healthy female controls were included. The mean age was 47.98 ± 6.90 years (range, 36–69 years) in the tamoxifen group and 48.57 ± 8.07 years (range, 34–72 years) in the control group, with no significant age difference between the groups ($p = 0.512$). The mean duration of tamoxifen therapy was 22.48 ± 13.41 months (range, 12–72 months). All patients were on a standard dose of 20 mg/day tamoxifen.

CVI measurements

The inter-rater agreement for the CVI values was high, with an ICC of 0.792. CVI values were 0.72 ± 0.05 and 0.73 ± 0.04 in the patient and control groups, respectively ($p = 0.916$).

Reflectivity measurements

The ICC values for TCA, LCA, and CVI were 0.783, 0.820, and 0.792, respectively, whereas the ICC values for the outer retinal reflectivity varied widely, ranging from 0.674 (nasal perifoveal EZ reflectivity) to 0.791 (foveal EZ reflectivity).

Reflectivity of the EZ at the central fovea and temporal perifovea was significantly lower in the tamoxifen group compared with controls ($p = 0.005$ and $p = 0.037$, respectively). Representative swept-source OCT B-scan images obtained from a tamoxifen-treated patient and an age-matched healthy control are shown in Fig. 3. No significant differences were observed in EZ reflectivity at the temporal parafovea, nasal perifovea, or nasal parafovea between the groups ($p > 0.05$ for all comparisons). Similarly, ELM and RPE reflectivity values at the central fovea, temporal perifovea, temporal parafovea, nasal perifovea, and nasal parafovea did not differ significantly between tamoxifen users and controls ($p > 0.05$ for all comparisons). Relative EZ reflectivity at the central fovea and temporal parafovea was also significantly lower in the tamoxifen group ($p = 0.012$ and $p = 0.039$, respectively). However, relative EZ reflectivity at the nasal parafovea, nasal perifovea and temporal perifovea, as well as relative ELM reflectivity at the central fovea, nasal parafovea, nasal perifovea, temporal parafovea, and temporal perifovea showed no significant group differences. Quantitative reflectivity measurements and relative reflectivity values of the ELM, EZ, and RPE are summarized in Table 1.

In the patient group, significant correlations were identified between outer retinal reflectivity measurements and indices of clinical exposure. The duration of therapy showed a weak positive and statistically significant correlation with both the absolute ($r = 0.389$, $p = 0.008$) and relative ($r = 0.426$, $p = 0.003$) ELM reflectivity at the central

Table 1 Comparison of choroidal vascular index and outer retinal reflectivity measurements between the patient and control groups

Parameter	Patient Group ($n=45$) Mean ± SD	Range (Min–Max)	Control Group ($n=50$) Mean ± SD	Range (Min–Max)	p
CVI	0.72 ± 0.05	0.61–0.84	0.73 ± 0.04	0.61–0.78	0.916
RPE reflectivity at central fovea (AU)	215.27 ± 9.46	194.97–234.89	216.90 ± 10.15	196.09–236.08	0.420
EZ reflectivity at central fovea (AU)	164.15 ± 21.21	117.81–199.75	175.71 ± 17.52	130.15–215.65	**0.005**
ELM reflectivity at central fovea (AU)	103.35 ± 11.75	74.88–139.73	105.69 ± 12.48	78.09–132.96	0.349
RPE reflectivity at nasal parafovea (AU)	212.57 ± 11.56	173.24–233.35	215.49 ± 10.04	194.28–238.75	0.191
EZ reflectivity at nasal parafovea (AU)	193.19 ± 18.61	147.54–220.43	199.36 ± 13.48	171.47–230.69	0.066
ELM reflectivity at nasal parafovea (AU)	110.37 ± 12.98	80.31–160.77	108.51 ± 13.75	73.89–135.39	0.499
RPE reflectivity at nasal perifovea (AU)	214.03 ± 8.81	194.03–230.90	214.24 ± 10.32	188.42–234.96	0.916
EZ reflectivity at nasal perifovea (AU)	194.38 ± 16.27	154.81–229.69	200.14 ± 13.41	158.70–223.30	0.065
ELM reflectivity at nasal perifovea (AU)	108.47 ± 15.05	76.82–154.66	108.90 ± 16.57	65.78–156.64	0.895
RPE reflectivity at temporal parafovea (AU)	211.51 ± 8.17	188.82–229.67	212.40 ± 9.82	190.06–232.36	0.633
EZ reflectivity at temporal parafovea (AU)	189.10 ± 17.86	107.16–224.84	195.54 ± 14.29	145.25–225.91	0.054
ELM reflectivity at temporal parafovea (AU)	105.95 ± 12.20	82.97–146.66	104.25 ± 11.55	83.86–125.55	0.490
RPE reflectivity at temporal perifovea (AU)	204.36 ± 11.33	170.91–228.78	207.03 ± 10.89	180.31–233.43	0.245
EZ reflectivity at temporal perifovea (AU)	183.17 ± 20.10	119.72–215.00	191.07 ± 16.32	149.39–218.84	**0.037**
ELM reflectivity at temporal perifovea (AU)	96.54 ± 10.88	77.52–128.25	97.97 ± 10.93	79.68–129.84	0.526
Relative ELM reflectivity at central fovea	0.48 ± 0.05	0.35–0.65	0.49 ± 0.05	0.38–0.63	0.500
Relative EZ reflectivity at central fovea	0.76 ± 0.10	0.58–0.94	0.81 ± 0.08	0.58–0.97	**0.012**
Relative ELM reflectivity at nasal parafovea	0.52 ± 0.05	0.43–0.70	0.50 ± 0.06	0.37–0.61	0.188
Relative EZ reflectivity at nasal parafovea	0.92 ± 0.08	0.74–1.17	0.93 ± 0.06	0.81–1.03	0.234
Relative ELM reflectivity at nasal perifovea	0.51 ± 0.07	0.37–0.70	0.51 ± 0.07	0.33–0.69	0.971
Relative EZ reflectivity at nasal perifovea	0.91 ± 0.07	0.74–1.02	0.94 ± 0.06	0.79–1.05	0.051
Relative ELM reflectivity at temporal parafovea	0.50 ± 0.05	0.41–0.66	0.49 ± 0.05	0.41–0.59	0.301
Relative EZ reflectivity at temporal parafovea	0.90 ± 0.07	0.54–1.02	0.92 ± 0.05	0.73–0.99	**0.039**
Relative ELM reflectivity at temporal perifovea	0.47 ± 0.05	0.39–0.61	0.47 ± 0.05	0.39–0.59	0.947
Relative EZ reflectivity at temporal perifovea	0.90 ± 0.08	0.70–1.02	0.92 ± 0.06	0.79–1.03	0.067

CVI, choroidal vascularity index; ELM, external limiting membrane; EZ, ellipsoid zone; RPE, retinal pigment epithelium; AU, arbitrary unit; SD, standard deviation

fovea. Age exhibited a statistically significant but weak negative correlation with absolute EZ reflectivity ($r = -0.331$, $p = 0.026$) and relative EZ reflectivity ($r = -0.388$, $p = 0.008$) in the nasal parafoveal region. No significant correlations were observed between RPE reflectivity in any quadrant or CVI and age or treatment duration. The correlation analysis between clinical parameters, CVI, and outer retinal layer reflectivity measurements in the patient group is presented in Table 2.

Among the reflectivity measurements across the central, parafoveal, and perifoveal regions, the difference between central foveal and nasal parafoveal relative ELM reflectivity was significantly greater in the patient group than the control group ($p = 0.047$). No significant differences were observed between the groups in any other region with respect to the reflectivity of the outer retinal layers. Reflectivity differences within and between the groups are presented in Table 3.

Discussion

In this prospective study, we evaluated the retinochoroidal effects of tamoxifen in breast cancer patients before any funduscopic or tomographic signs of toxicity became apparent. Our findings indicated that tamoxifen use was associated with reduced foveal EZ reflectivity and a statistically significant increase in ELM reflectivity with longer treatment duration. The results may suggest preliminary structural alterations in the outer retinal layers of tamoxifen-treated individuals, aiding in the understanding of early pre-toxic retinal alterations and potentially contributing to future monitoring strategies.

The evaluation of macular involvement is essential in tamoxifen toxicity, as the earliest alterations are most likely to manifest in this region. Although many studies have reported macular alterations related to tamoxifen, their pathophysiological basis, and which retinal layers are primarily affected, has not yet been fully clarified [6–9]. Several investigations have documented degenerative changes affecting the photoreceptors and the RPE, suggesting involvement of the outer retina, whereas others have proposed that Müller cell dysfunction plays a pivotal role in the pathophysiology [6, 7]. Considering these findings, the functional and structural integrity of the ELM, EZ, and RPE layers appears to be crucial for understanding the underlying disease mechanisms.

Crisóstomo et al. [19] evaluated OCT and OCT-angiography (OCT-A) findings in one hundred tamoxifen-treated patients, assessing the effects of tamoxifen on

Table 2 Spearman's correlation analysis of clinical parameters and choroidal vascular index and outer retinal layer reflectivity measurements in the patient group

Parameters	Age		Duration of therapy	
	r	*p*	*r*	*p*
CVI	0.198	0.192	0.185	0.225
ELM central fovea	0.045	0.768	0.389	**0.008**
EZ central fovea	-0.102	0.506	0.155	0.310
RPE central fovea	0.090	0.557	-0.073	0.632
ELM para N	-0.101	0.505	0.165	0.278
EZ para N	-0.331	**0.026**	0.101	0.506
RPE para N	-0.034	0.820	0.023	0.876
ELM peri N	-0.219	0.146	0.220	0.145
EZ peri N	-0.138	0.365	0.016	0.916
RPE peri N	0.013	0.930	0.190	0.210
ELM para T	-0.023	0.877	0.220	0.145
EZ para T	0.123	0.418	0.242	0.108
RPE para T	0.095	0.532	0.159	0.295
ELM peri T	0.222	0.141	-0.028	0.854
EZ peri T	-0.074	0.626	0.104	0.496
RPE peri T	0.184	0.225	-0.240	0.111
Rel ELM central fovea	-0.015	0.922	0.426	**0.003**
Rel EZ central fovea	-0.176	0.246	0.186	0.219
Rel ELM para N	-0.056	0.711	0.235	0.120
Rel EZ para N	-0.388	**0.008**	0.160	0.293
Rel ELM peri N	-0.204	0.178	0.144	0.343
Rel EZ peri N	-0.120	0.430	-0.083	0.586
Rel ELM para T	-0.106	0.488	0.196	0.194
Rel EZ para T	0.052	0.730	0.194	0.201
Rel ELM peri T	0.182	0.229	0.011	0.938
Rel EZ peri T	-0.232	0.123	0.209	0.166

Abbreviations: CVI choroidal vascular index, ELM external limiting membrane, EZ ellipsoid zone, RPE retinal pigment epithelium, Para parafoveal, Peri perifoveal, N nasal, T temporal, Rel relative

individual retinochoroidal layers. A notable feature of their study was that it was performed on patients devoid of any apparent retinal disease. They revealed reductions in total macular thickness, particularly involving the RPE. The authors proposed that these structural changes may reflect subclinical involvement of the outer retina, particularly at the level of the RPE and photoreceptors. In contrast, no RPE alteration was detected in our cohort, a finding that may be explained by the shorter treatment duration, lower cumulative tamoxifen exposure, and the smaller sample size in our study.

Bicer et al. [20] used fundus reflectometry to compare tamoxifen-treated patients with controls and found reduced macular pigment optical density in the tamoxifen group. Macular pigments are densely concentrated in the fovea and are present within retinal structures that contribute to photoprotection, including the outer retina. The research suggests early vulnerability of macular pigment due to tamoxifen exposure, potentially consistent with metabolic involvement in the outer retina, despite unchanged standard structural metrics. In our study, the decrease in EZ reflectivity may similarly represent an early sign of tamoxifen-associated outer retinal involvement in the macular region. In a case series, Ritter et al. [21] also reported that tamoxifen-treated patients, despite having unremarkable fundus examinations, demonstrated central amplitude reduction and generalized retinal dysfunction on multifocal ERG. These findings may indicate that tamoxifen affects the outer retina.

Oskan et al. [17] assessed the reflectivities of the ELM, EZ, and RPE layers in 33 patients diagnosed with central serous chorioretinopathy and examined their correlation with subretinal fluid characteristics. The study found that increased fluid volume and extended disease duration correlated with decreased EZ reflectivity, which the authors linked to disruption between photoreceptor and RPE. Our study also observed a reduction in foveal EZ reflectivity. The EZ layer reflects the elevated mitochondrial density within the inner segments of photoreceptors. As tamoxifen has been linked to mitochondrial dysfunction and disrupted oxidative phosphorylation, a decrease in EZ reflectivity may serve as an early optical indicator of bioenergetic stress within the photoreceptor–RPE complex [22]. An additional finding was the increase in ELM reflectivity associated with longer treatment duration. The formation of the ELM enhancement at the junction of photoreceptors and Müller cells suggests that an early stress response resulting from photoreceptor impairment may play a role in this observation. Müller cell dysfunction, commonly described in the context of tamoxifen-related retinal toxicity, may contribute to heightened ELM reflectivity, indicating that the ELM is particularly responsive to outer retinal changes due to tamoxifen exposure.

Over the past years, considerable variability in choroidal thickness measurements has been reported across studies. On the other hand, the CVI has been identified as a more reliable parameter for quantifying the vascular and stromal components of the choroid in various retinochoroidal diseases and drug-related toxicities [11, 14, 15]. Long-term assessments of choroidal thickness in patients treated with tamoxifen have produced inconsistent findings regarding toxicity, with certain studies indicating choroidal thickening while others report choroidal thinning [8, 19]. However, only a few studies have specifically evaluated CVI in tamoxifen users. Crisóstomo et al. [19] evaluated choroidal vascular parameters, such as choroidal thickness, TCA, LCA, and CVI, in patients treated with tamoxifen, observing significant reductions across all indices. These changes were attributed to impaired choroidal perfusion, consistent with experimental data indicating that tamoxifen can lower extracellular vascular endothelial growth factor levels, reduce vascular smooth muscle cell proliferation through

Table 3 Reflectivity differences within and between the groups

	Patient group difference					Control group difference					Patient vs. Control
	Mean	SD	95% CI		*p*	Mean	SD	95% CI		*p*	*p*
EZc vs. EZ para T	-24.95	18.93	-30.64	-19.27	< 0.001	-19.83	17.70	-24.86	-14.80	< 0.001	0.176
EZc vs. EZ para N	-29.04	20.24	-35.12	-22.95	< 0.001	-23.65	16.69	-28.39	-18.90	< 0.001	0.158
EZc vs. EZ peri T	-19.02	23.45	-26.06	-11.97	< 0.001	-15.36	19.46	-20.89	-9.83	< 0.001	0.409
EZc vs. EZ peri N	-30.22	24.60	-37.62	-22.83	< 0.001	-24.43	18.13	-29.58	-19.27	< 0.001	0.191
ELMc vs. ELM para T	-2.60	9.79	-5.54	0.34	0.082	1.44	12.01	-1.97	4.85	0.400	0.077
ELMc vs. ELM para N	-7.03	10.99	-10.33	-3.72	< 0.001	-2.81	10.57	-5.82	0.19	0.066	0.060
ELMc vs. ELM peri T	6.80	13.89	2.63	10.98	0.002	7.72	12.16	4.27	11.18	< 0.001	0.732
ELMc vs. ELM peri N	-5.12	13.80	-9.27	-0.97	0.017	-3.20	13.36	-7.00	0.59	0.096	0.494
RPEc vs. RPE para T	3.76	8.79	1.12	6.40	0.006	4.50	9.63	1.76	7.24	0.002	0.697
RPEc vs. RPE para N	2.70	13.10	-1.24	6.64	0.174	1.42	7.93	-0.84	3.67	0.213	0.560
RPEc vs. RPE peri T	10.90	10.68	7.70	14.11	< 0.001	9.87	11.22	6.68	13.06	< 0.001	0.648
RPEc vs. RPE peri N	1.24	9.59	-1.64	4.12	0.390	2.67	12.56	-0.90	6.23	0.140	0.539
relEZc vs. relEZperi T	-0.13	0.10	-0.16	-0.10	< 0.001	-0.11	0.10	-0.14	-0.08	< 0.001	0.300
relEZc vs. relEZpara T	-0.13	0.10	-0.16	-0.10	< 0.001	-0.11	0.09	-0.14	-0.08	< 0.001	0.281
relEZc vs. relEZperi N	-0.15	0.12	-0.18	-0.11	< 0.001	-0.12	0.09	-0.15	-0.10	< 0.001	0.310
relEZc vs. relEZpara N	-0.15	0.11	-0.18	-0.11	< 0.001	-0.11	0.08	-0.14	-0.09	< 0.001	0.107
relELMc vs. relELMperi T	0.01	0.06	-0.01	0.03	0.410	0.01	0.06	-0.01	0.03	0.089	0.582
relELMc vs. relELMpara T	-0.02	0.05	-0.04	-0.01	0.007	-0.01	0.06	-0.02	0.01	0.725	0.130
relELMc vs. relELMperi N	-0.03	0.07	-0.05	-0.01	0.010	-0.02	0.06	-0.04	-0.01	0.019	0.595
relELMc vs. relELMpara N	-0.04	0.06	-0.056	-0.02	< 0.001	-0.02	0.05	-0.03	-0.01	0.023	**0.047**

ELM, external limiting membrane; EZ, ellipsoid zone; RPE, retinal pigment epithelium; Para, parafoveal; Peri, perifoveal; C, central; N, nasal; T, temporal, Rel relative, SD standard deviation

TGF-β modulation, and diminish endothelial vasodilatory responses to nitric oxide. A systematic review and meta-analysis conducted by Homayuni et al. [23] also revealed a significant decrease in foveal deep capillary plexus vessel density among tamoxifen-treated patients in comparison to healthy controls, indicating a notable neurovascular aspect of tamoxifen toxicity. In contrast, we did not observe any significant differences in choroidal parameters between tamoxifen-treated patients and healthy controls. The lack of observable changes in our cohort may be attributed to the younger mean age of the patient group and the shorter treatment duration, leading to reduced cumulative tamoxifen exposure and potentially a diminished cumulative vascular insult to the choroid.

We assessed the reflectivity variations among the central fovea and the nasal and temporal parafoveal and perifoveal regions, subsequently comparing the extent of these variations between the patient and control groups. While a variation in reflectivity away from the foveal center is a recognized physiological pattern in healthy individuals, our objective was to assess whether tamoxifen-treated patients displayed a more significant deviation from this typical gradient-specifically, whether the

outer retinal layers demonstrated a greater change in reflectivity from the central fovea to the parafoveal or perifoveal quadrants in comparison to controls. The only significant reflectivity change was a reduction between central foveal relative ELM reflectivity and nasal parafoveal relative ELM reflectivity. The results suggest that tamoxifen does not selectively target the central, parafoveal, or perifoveal zones. The alteration in reflectivity appears to represent a more diffuse effect on the outer retina, while the physiological spatial pattern of reflectivity remains largely intact.

This study has several limitations. First, it was conducted at a single center, which may limit the generalizability of the findings. Second, the sample size was relatively small. Third, the absence of OCT-A and EDI-OCT imaging restricted the depth of choroidal vascular assessment. Moreover, even though two independent graders evaluated the measurements, reflectivity and choroidal vascular assessments depend on image quality and segmentation accuracy; therefore, some variability is inevitable despite strict quality control. Another limitation is that multiple statistical comparisons were performed across several retinal subregions and reflectivity parameters without formal correction for multiplicity. Therefore, particularly the findings with borderline p-values should be interpreted cautiously, and future studies with larger cohorts are needed to validate these observations.

On the other hand, to our knowledge, this is the first study to evaluate outer retinal reflectivity changes that may detect very early alterations in tamoxifen users before any observable fundus or OCT abnormalities, which represents a key strength of our work. Tamoxifen is extensively utilized in the management of breast cancer, a condition associated with mortality risk. Due to the lack of clearly defined ocular toxicity thresholds compared to many other medications, standardized intervals for ophthalmic monitoring have not been firmly established. Considering the potential for retinopathy associated with tamoxifen use, identifying early changes in outer retinal reflectivity prior to clinically detectable visual dysfunction may improve understanding of early retinal involvement and may contribute to future risk stratification and monitoring approaches. However, longitudinal studies are required before these findings can be translated into clinical follow-up recommendations.

This study suggests that early tamoxifen exposure is associated with reduced EZ reflectivity and subtle, treatment-duration-related variation in ELM reflectivity, thereby highlighting early involvement of the outer retinal layers and suggesting subclinical photoreceptor dysfunction. Further studies with larger cohorts and longitudinal follow-up are necessary to validate these findings and clarify the potential clinical relevance of outer retinal reflectivity assessments in tamoxifen-associated retinal toxicity.

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Author contributions
BHU and CDE contributed to the conception and design of the study. BHU and SK participated in the acquisition, analysis, and interpretation of the data. BHU drafted the manuscript. SK, CDE, and UV critically revised the manuscript for important intellectual content.

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Data availability
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This prospective study was conducted at Izmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital in accordance with ethical standards and the principles of the Declaration of Helsinki. The Clinical Research Ethics Committee of Izmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital approved the study protocol (decision number 2025/466, date: 02.06.2025). Comprehensive information about the study procedures was provided to all participants and written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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