• Clinical Research •

Hypercortisolism and ocular microcirculation: exploring retinal and choroidal remodeling in Cushing's disease

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Abstract

● **AIM:** To investigate the potential of optical coherence tomography angiography (OCTA) for detecting subclinical microvascular damage, possibly before ocular complications develop, in treatment-naive Cushing's disease (CD) patients.

● **METHODS:** This retrospective cross-sectional study included 48 newly diagnosed, treatment-naive CD patients and 48 healthy controls. Ophthalmological examinations, including best-corrected visual acuity, intraocular pressure, optical coherence tomography (OCT), and OCTA were conducted. Retinal and choroidal vessel density (VD) parameters were assessed in the macular and peripapillary regions. Correlations between VD and systemic hormone levels were analyzed.

● **RESULTS:** Age (47.3±13.3y *vs* 43.4±15.8y; *P*=0.053) and gender distribution (CD: 35 females, 13 males; controls: 34 females, 14 males; *P*=1.000) did not significantly differ. Patient group exhibited significant reductions in radial peripapillary capillary (RPC; *P*<0.05) and choriocapillaris (CC) VD across all quadrants (*P*<0.05) compared to controls. Nasal deep capillary plexus (DCP) VD was also significantly decreased (*P*=0.035). Subfoveal choroidal thickness (SFCT; *P*=0.459) did not differ significantly, but nasal choroidal thickness (CT) at 1500 μm (*P*<0.040) and 3000 μm (*P*<0.031) was markedly increased. Notably, hormonal correlations revealed associations between ACTH and temporal CC VD (*r*=0.367, *P*=0.009), plasma cortisol and superior RPC VD (*r*=0.303, *P*=0.034), and urinary free cortisol with superior, and nasal RPC (*r*=-0.404, *P*=0.004, *r*=-0.317, *P*=0.027) and nasal DCP VD (*r*=-0.287, *P*=0.045).

● **CONCLUSION:** High endogenous cortisol levels in CD patients primarily affect the peripapillary region and the nasal part of the macula. VD changes occur before pachyvessel formation, choroidal thickening, and the development of pachychoroid spectrum disorder.

● **KEYWORDS:** Cushing's disease; optical coherence tomography angiography; hypercortisolism; microvascular changes

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INTRODUCTION

Cushing's syndrome (CS) is a serious endocrine disorder caused by excessive cortisol production, primarily due to adrenocorticotropic hormone (ACTH)-secreting pituitary tumors, with rarer causes including ectopic ACTH-secreting or adrenal tumors[1]. This rare condition affects 12-62 individuals per million, with an annual incidence of 1-3 per million[2]. A subset of CS, Cushing's disease (CD), results from excessive ACTH secretion due to a pituitary adenoma (PA)[1]. These tumors are often microadenomas. Unlike other CS forms, CD rarely causes symptoms from local mass effects and is typically identified through clinical manifestations of hypercortisolism.

Elevated cortisol levels contribute to systemic complications such as obesity, hypertension, dyslipidemia, and osteoporosis[3]. Beyond systemic effects, CD also impacts ocular health, leading to ocular hypertension, exophthalmos, and cataracts. Additionally, increased cortisol levels are linked to the pachychoroid disease spectrum (PDS)[4], which includes conditions like central serous chorioretinopathy (CSC), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), polypoidal choroidal vasculopathy (PCV), and peripapillary pachychoroid syndrome (PPS). These disorders share features such as choroidal vascular hyperpermeability, venous dilation, vortex vein anastomoses, and delayed choroidal venous filling. Advances in ocular imaging have clarified the relationship between hypercortisolism and PDS[5-7].

Although literature suggests a link between elevated cortisol and retinochoroidal disorders, the association between CD and retinal microvascular changes, assessed *via* optical coherence tomography angiography (OCTA), remains underexplored[4,8-9]. Given the limited research and patient availability, our study aims to bridge this gap by using OCTA to investigate macular and peripapillary alterations in treatment-naive CD patients, offering insight into the ocular vascular effects of hypercortisolism. Additionally, OCTA may prove valuable in the early diagnosis, monitoring, and treatment follow-up of CD, potentially enabling early detection of vascular changes before overt disease manifestations occur.

PARTICIPANTS AND METHODS

Ethical Approval This cross-sectional study included treatment-naive, active CD patients in a hypercortisolemic state, monitored in endocrinology and ophthalmology clinics (August 2020–November 2024). The study was approved by the Institutional Review Board prior to its initiation (IRB Approval No: E-96317027-514.10-260893749). It was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Eligibility required a confirmed diagnosis of active CD based on endocrinologist-conducted blood tests, magnetic resonance imaging (MRI) confirmed PA, and non-suppressed serum cortisol after a low-dose dexamethasone suppression test (serum cortisol >1.8 μg/dL or 50 mmol/L) along with at least one altered first-line screening test [24-hour urinary free cortisol (UFC), nocturnal serum cortisol, or late-night salivary cortisol], repeated twice to minimize false negatives. ACTH levels, pituitary MRI, and, if needed, inferior petrosal sinus sampling, were used to confirm pituitary CD.

The control group comprised healthy volunteers who provided informed consent. Only right eyes were included. Inclusion required normal biomicroscopic, fundoscopic, and optic nerve evaluations. Exclusion criteria for both groups included visual acuity <20/25 (Snellen), pre-existing corneal disease, contact lens use, history of systemic/ocular diseases or surgery, chronic topical medication use, glaucoma, retinal nerve fiber layer (RNFL) defect, visual field defect, refractive errors ≥4 D, ocular trauma, uveitis, strabismus, nystagmus, or pregnancy. Additional exclusions included prior PA surgery, CD medication use (except <1mo pre-surgery), central nervous system diseases, ocular abnormalities affecting vision.

A single ophthalmologist (Yilmaz YC) conducted ophthalmological examinations, including best-corrected visual acuity (BCVA; logMAR), intraocular pressure (IOP), and fundus examination, followed by standard automated perimetry, optical coherence tomography (OCT), and OCTA. Central macular thickness (CMT), subfoveal choroidal thickness (SFCT), and OCTA imaging were performed using Topcon DRI OCT Triton Swept Source-OCT (Topcon Corporation, Tokyo, Japan).

OCT images covered a 6 mm×6 mm area of the disc and a 7 mm×7 mm macular area, ensuring proper centering and segmentation. Macular OCTA scans (6 mm×6 mm, 320 B-scans) were centered on the fovea. To ensure accurate magnification correction for each participant, individual biometric values including axial length, corneal curvature, and spherical equivalent were manually entered into the device through the user-accessible input interface prior to image acquisition[10]. The Topcon Triton software then automatically adjusted the scaling of each OCT and OCTA image based on the entered biometric parameters. This correction method was applied to all measurements to eliminate inter-individual variability related to ocular magnification.

Choroidal thickness (CT) and pachyvessel presence were evaluated by two independent, blinded physicians (Yilmaz YC and Hayat SC). Intraclass correlation coefficients with 95% confidence intervals were calculated for intergrader agreement. Measurements were taken along a horizontal section through the fovea at subfoveal, 1500 μm nasal and temporal (nasal, temporal CT 1), and 3000 μm nasal and temporal (nasal, temporal CT 2) locations (Figure 1A).

IMAGEnet 6 software (Topcon Corporation, Japan; version 1.21.11783) generated en face slabs for measuring superficial retinal capillary plexus (SCP), deep retinal capillary plexus (DCP), and choriocapillaris (CC) vessel density (VD) (Figure 1C-1E).

Peripapillary OCTA scans covered a 4.5 mm×4.5 mm area around the optic disc, with the radial peripapillary capillary (RPC; Figure 1B) segment extending from the internal limiting membrane (ILM) to the posterior boundary of the RNFL. To minimize diurnal variations in CT, measurements were taken between 12:00 *a.m.* and 2:00 *p.m.*, a time period when the diurnal fluctuations are typically at their minimal and closest to the mean CT value[11]. SFCT was measured from the high-reflection zone of Bruch's membrane under the retinal pigment epithelium (RPE) to the outer choroidoscleral boundary. Sattler's and Haller's layers were manually assessed based on choroidal vessel morphology. Pachychoroid was defined as choroidal thickening on OCT with dilated large vessels and compression of Sattler's layer and CC[12].

Statistical Analysis Statistical analysis was performed using SPSS 25.0 (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test assessed data distribution. Descriptive statistics were presented as mean±standard deviation or median (range). Categorical variables were analyzed with the Chi-squared test. Correlations were evaluated using Spearman's rho test. Depending on normality, intergroup comparisons were

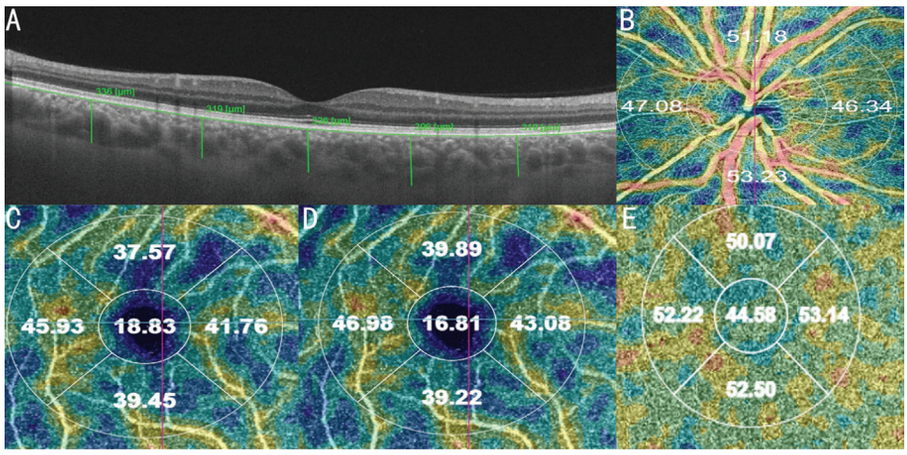

Figure 1 Structural OCT and OCTA images demonstrated CT and VD across the RPC, SCP, DCP, and CC layers A: OCT image and CT measurements; B: RPC VD; C: SCP VD; D: DCP VD; E: CC VD. OCT: Optical coherence tomography; OCTA: OCT angiography; CT: Choroidal thickness; VD: Vessel density; RPC: Radial peripapillary capillaries; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CC: Choriocapillaris.

conducted *via* the *t*-test or Mann-Whitney *U* test. Statistical significance was set at $P<0.05$.

RESULTS

Demographic and Baseline Characteristics A total of 48 CD patients and 48 controls were included. Age (47.3±13.3y *vs* 43.4±15.8y; $P=0.053$) and gender distribution (CD: 35 females, 13 males; controls: 34 females, 14 males; $P=1.000$) did not significantly differ.

Macular and Choroidal Thickness CMT (266.1±26.1 μm *vs* 272.9±23.3 μm; $P=0.459$) and SFCT (301.9±45.4 μm *vs* 294.6±30.8 μm; $P=0.459$) showed no significant differences. However, nasal CT 1 and nasal CT 2 were significantly higher in CD patients (Table 1).

Vessel Density Measurements CD patients had significantly lower RPC density compared to controls (Table 2). CC density was also significantly reduced in all quadrants, with a notable nasal DCP decrease (Table 3). No significant differences were found in SCP density.

Correlations Serum cortisol (57.2±19.7 μg/dL), ACTH (163.6±115.5 pg/mL), and 24-hour UFC (304.9±133.5 μg/24h) were evaluated. Significant correlations: temporal CC density correlated with ACTH ($r=0.367$, $P=0.009$). Plasma cortisol correlated with superior RPC density ($r=0.303$, $P=0.034$). UFC correlated with superior RPC ($r=-0.404$, $P=0.004$), nasal RPC ($r=-0.317$, $P=0.027$), and nasal DCP values ($r=-0.287$, $P=0.045$). No significant correlations were found between serum/urinary hormone levels and CT or CMT.

No significant correlation between glycated hemoglobin (HbA1c) or mean arterial pressure and CT in the patient group. HbA1c significantly correlated with: temporal DCP ($r=-0.311$, $P=0.032$), inferior DCP ($r=-0.306$, $P=0.035$), nasal DCP VD ($r=-0.303$, $P=0.036$).

Pachychoroid Disease Spectrum Features Pachyvessels were detected in 33 eyes (68.7%) in the CD group, with 23

Table 1 CT in CD *vs* controls

CT (μm)	CD	Controls	*P*
Subfoveal	301.9±45.4	294.6±30.8	0.459[a]
Nasal 1	312±58.5	288±54.4	<0.040[b]
Nasal 2	311±58.6	292.2±74.9	<0.031[a]
Temporal 1	288.2±56.4	282.3±40.2	0.558[b]
Temporal 2	299.7±51.7	282.6±40.9	0.076[b]

CT: Choroidal thickness; CD: Cushing's disease. [a]Mann-Whitney *U* test; [b]*t*-test.

Table 2 RPC VD in CD *vs* controls

VD (%)	CD	Controls	*P*
RPC superior	53.8±4.2	55.6±3.3	0.036[a]
RPC temporal	50.6±5.4	53.0±3.2	0.004[a]
RPC inferior	53.8±3.0	55.3±2.3	0.006[a]
RPC nasal	50.8±4.5	53.7±3.0	0.001[a]

RPC: Radial peripapillary capillary; VD: Vessel density; CD: Cushing's disease. [a]Mann-Whitney *U* test.

Table 3 VD in SCP, DCP, and CC in CD *vs* controls

VD (%)	CD	Controls	*P*
SCP whole	17.1±3.6	18.2±3.4	0.158[b]
SCP superior	48.1±5.4	48.9±5.6	0.237[a]
SCP temporal	44.4±4.5	45.7±3.9	0.086[a]
SCP inferior	43.8±7.5	46.2±5.1	0.080[a]
SCP nasal	45.2±5.2	46.4±3.8	0.209[a]
DCP whole	18.8±3.9	19.1±3.2	0.661[b]
DCP superior	45.0±5.0	45.2±6.0	0.160[a]
DCP temporal	46.9±5.7	47.8±5.5	0.098[a]
DCP inferior	45.2±7.2	46.3±3.9	0.290[a]
DCP nasal	46.8±7.0	48.8±4.4	0.035[a]
CC whole	50.7±54.3	53.2±2.6	<0.001[a]
CC superior	51.3±2.4	51.7±3.3	0.023[a]
CC temporal	52.1±3.0	53.3±2.2	0.007[a]
CC inferior	51.5±2.3	53.1±2.1	<0.001[b]
CC nasal	51.3±2.5	52.8±2.6	<0.001[a]

VD: Vessel density; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CC: Choriocapillaris; CD: Cushing's disease. [a]Mann-Whitney *U* test; [b]*t*-test.

eyes (47.9%) exhibiting PDS findings: PPS: 3 eyes (6.6%), CSC: 6 eyes (12.5%), PPE: 14 eyes (29.16%), uncomplicated pachychoroid: 10 eyes (20.8%), no pachyvessels: 15 eyes (31.3%).

Comparisons between patients with and without pachyvessels showed no significant differences in age, serum/urinary hormone levels, or CMT parameters. CT was significantly higher in the pachyvessel group in all measured quadrants (Table 4). All CC density values were significantly lower in the pachyvessel-positive group compared to healthy controls, whereas in the pachyvessel-negative group, only temporal, inferior, and nasal CC densities were lower compared to controls (P<0.05). Additionally, in the pachyvessel-positive group, RPC densities were significantly reduced in all quadrants, whereas in the pachyvessel-negative group, only the inferior and temporal RPC values were significantly lower compared to the control group (P<0.05). In the pachyvessel positive group, nasal DCP and SCP whole densities were found to be significantly lower compared to the control group (P<0.05). In contrast, no significant retinal microvascular changes were observed in the pachyvessel negative group.

Table 4 Comparison of clinical and ocular parameters in patients with and without pachyvessels

Parameters	Pachyvessels+ (n=33)	Pachyvessels- (n=15)	P
Age (y)	48.6±14.0	44.4±11.8	0.367[a]
Serum cortisol (μg/dL)	60.1±18.8	58.2±22.8	0.681[a]
ACTH (pg/mL)	168.1±114.2	153.7±121.8	0.266[a]
UFC-24h (μg/24h)	318.8±83.7	331.2±189.4	0.291[a]
CT (μm)			
Subfoveal CT	315.2±45.9	272.5±27.3	0.001[a]
Nasal 1 CT	334.5±52.4	262.4±37.2	<0.001[b]
Nasal 2 CT	337.2±47.7	253.2±33.5	<0.001[b]
Temporal 1 CT	307.2±55.5	246.2±29.9	<0.001[b]
Temporal 2 CT	316.9±49.6	262.0±33.6	<0.001[b]
CMT	263.3±25.5	272.1±27.5	0.193[a]

ACTH: Adrenocorticotropic hormone; UFC-24h: 24-hour urinary free cortisol; CT: Choroidal thickness; CMT: Central macular thickness. [a]Mann-Whitney U test, [b]t-test.

DISCUSSION

The PDS is observed across a spectrum of conditions that share similar clinical characteristics and etiological features[7]. These features including pachychoroid, pachyvessels, and increased vascular hyperpermeability, which contribute to significant venous overload[12-13]. Increased psychological stress, sympathetic activity, type A personality have been previously described as risk factors of PDS. Increased cortisol levels are also linked to the development of PDS[14]. CD is an endocrine disease characterized by excessive endogenous cortisol secretion[15]. Previous studies have shown that findings of PDS can develop in patients with CD[4,16-18].

Upon reviewing the previous studies in the literature, Eymard *et al*[16] found no significant difference in SFCT between CS patients and controls, whereas other studies reported increased SFCT in CS[4,17-18]. Duan *et al*[9] observed a significant reduction in CT post-adrenalectomy, while Lassandro *et al*[19] reported higher SFCT in CD. Similarly, Abalem *et al*[4] noted increased CT in CS but based on a small cohort with longer disease duration. Interestingly, Eymard *et al*[16] found higher SFCT in adrenal-origin CS than in CD, consistent with Wang *et al*'s[18] findings. In our study, SFCT did not differ significantly; however, nasal 1 and nasal 2 CT were higher in CD patients. These discrepancies may stem from etiology differences and the shorter disease duration in our cohort.

In patients with PDS, simultaneous elevations in CT and cortisol levels have been observed, and CT diurnal variations mirror plasma cortisol rhythms[20]. However, Eymard *et al*[16] found no significant association between CT and cortisol levels, and Wang *et al*[18] reported that a connection between endogenous cortisol and CT remains unproven. While they found a correlation between SFCT and 24-hour UFC in CS patients, our study did not replicate this finding. Karaca *et al*[17] reported no significant relationship between SFCT and cortisol levels but found a correlation with ACTH. Given that ACTH receptors are primarily in the adrenal cortex while cortisol receptors are widely distributed, including in the choroid, these findings require careful interpretation[17]. Some CS patients with adrenal-origin disease, despite suppressed ACTH, exhibited increased SFCT, suggesting additional influencing factors. To minimize diurnal variation effects, OCT measurements were conducted in the afternoon. Despite this, no significant correlation was found between SFCT and cortisol levels. This may be due to our cohort's restriction to newly diagnosed, pituitary-origin patients and pre-treatment evaluations. Additionally, CT changes from endogenous cortisol may require prolonged exposure, as seen in PDS[21]. In severe cases, vessels within Haller's layer may dominate CT, and eyes with normal CT may later develop a pachychoroidal phenotype due to outer choroidal vessel expansion and inner choroidal atrophy[12]. Given the eye's localized cortisol metabolism, ocular cortisol levels might be more relevant than systemic measurements for detecting ocular changes.

In addition to inner choroid attenuation, thinning of the retinal layers has been documented in PDS. Chronic choroidal ischemia in PNV has been linked to vessel loss in the SCP and DCP[22]. Mao *et al*[23] reported reduced DCP density in chronic PDS, while Akkoc *et al*[24] found similar reductions, noting a positive correlation between parafoveal DCP density and CMT. Since the DCP supplies oxygen to photoreceptors, reduced DCP density may explain decreased CMT[25]. However, in our study, DCP reduction was observed only in the nasal region,

likely explaining the absence of generalized CMT reduction. Duan *et al*[9] found increased CMT in CS patients post-surgery, suggesting that choroidal vasodilation and hyperperfusion, secondary to high cortisol, may lead to excessive oxygen supply. Following surgery, relative hypoxia in the retina may lead to retinal thickening. Duan *et al*'s[9] univariate analysis also linked CMT changes to CS duration and 24h-UFC levels, implying that insufficient choroidal perfusion post-surgery plays a role. Based on our findings and existing literature, we conclude that structural changes in CMT and SFCT require prolonged disease progression to become evident.

Analysis of OCTA parameters has primarily focused on assessing the flow and VD of the CC to evaluate ischemia. Studies have demonstrated flow deficits in the CC layer during the early and uncomplicated stages of PDS[26-28]. A correlation between CC density and the location of pachyvessels has also been identified, supporting the hypothesis that pachyvessels exert mechanical pressure on the CC, leading to ischemia, which is consistent with our findings. Interestingly, previous literature has declared that CC flow and density were higher in the PPE group than in the CSC group, with the highest levels observed in the uncomplicated pachychoroid group[29]. This suggests that these effects are a consequence of chronic choroidal ischemia and demonstrate the progressive nature of the disease itself.

With this in mind, we examined retinal and choroidal vascular characteristics in CD. While numerous studies assess CT, research on retinal plexus in this population is limited[9,19]. Our study found significantly lower RPC in all quadrants and reduced CC density in patient group, with a notable decrease in nasal DCP. Only two prior studies have evaluated macular and choroidal VD in CS using OCTA. Lassandro *et al*[19] reported higher CC density in patients than controls, while Duan *et al*[9] found no significant changes in superficial or deep plexus density after surgery, though CC flow area decreased and correlated with 24h-UFC[9,19]. In contrast, we observed lower CC density in patient group, likely due to methodological differences. Our study included only newly diagnosed, treatment-naive patients with active hypercortisolism, assessed before treatment. Duan *et al*'s[9] study had just 17 patients, all with adrenocortical carcinoma, while Lassandro *et al*'s[19] cohort had longer disease durations (95mo), including both active and inactive cases[9,19]. Lassandro *et al*[19] suggested increased CT and pachyvessels in the Haller layer may precede choroidal ischemia, termed uncomplicated pachychoroid. However, given their long disease duration, this phase is unlikely to represent early PDS. Patients may have experienced various PDS stages, with pathological findings resolving post-treatment. Baek *et al*[27] and Demirel *et al*[29] proposed that CC flow impairment near pachyvessels may exist before RPE or outer retinal changes, with a gradual expansion of signal deficit over time. The literature consistently supports choroidal flow reduction as an early PDS effect[26-28]. Based on our findings, the increased choroidal density observed by Duan *et al*[9] and Lassandro *et al*[19] after treatment likely represents a reactive remodeling response following prolonged high-dose cortisol exposure.

Additionally, while both the pachyvessel and non-pachyvessel groups demonstrated reduced peripapillary and choroidal VD values compared to controls, a significant increase in CT was observed only in the pachyvessel group in our study. This suggests that endogenous cortisol may initially decrease the peripapillary and choroidal VD, and as the involvement progresses across all quadrants, it may lead to the formation of pachyvessels and a subsequent increase in CT. Retinal microvascular changes appear to occur at a later stage in this process. The proportion of patients exhibiting PDS features other than PPE was 19%. This indicates that, despite elevated cortisol levels, a significant proportion of patients did not show clinical signs of the disease. The absence of changes in SFCT and CMT across all patients, alongside the changes in RPC and CC density values observed in OCTA, underscores the value of OCTA as a tool for detecting subclinical vascular damage in the early period of CD. Future large-scale studies may demonstrate that OCTA can help identify such changes before the onset of disease manifestations, potentially enabling early intervention and prevention of adverse outcomes. Although our findings are the first in the literature and differ from previous studies, they must be interpreted with caution due to the relatively small overall patient sample size and the further reduction in the number of patients within subgroup analyses[9,19].

Apaydin *et al*[30] assessed microvascular structure in active and remission stages of CS, reporting lower capillary count and increased limb diameter and capillary width, independent of disease activity or hormone levels but significantly linked to body mass index, diabetes mellitus, and HbA1c. Literature indicates about 50% variability in UFC across samples, with greater fluctuations at higher levels. No linear correlation was found between mean UFC levels and hypercortisolism-related features, such as fasting glucose, HbA1c, insulin resistance, or mean arterial pressure, with severity likely tied more to duration than cortisol levels[31]. These findings underscore the need for cautious interpretation when correlating VD with serum or urinary cortisol in our study.

PPS is a distinct variant of PDS, characterized by maximum CT near the optic nerve rather than subfoveally[32]. In this condition, large choroidal vessels are more prominent nasally than temporally. It is plausible that hypercortisolism remodels the RPE/choroid complex rather than directly affecting SFCT,

with changes appearing earlier in the nasal choroid. Several mechanisms have been proposed, including peripapillary choroidal congestion leading to elevated hydrostatic pressure and impaired RPE function. Disrupted choroidal outflow may compress the optic nerve, contributing to PPS. Acquired lamina cribrosa defects may further exacerbate this effect[33-35]. Histological studies suggest increased resistance in choroidopial or vortex veins contributes to PPS. Additionally, the absence of RPE around the optic nerve may allow hydrostatic pressure to transmit directly to the inner retina[36]. While PDS is typically associated with reduced capillary density and CMT, our study did not find significant SCP or CMT reductions[22-25]. However, SFCT remained unchanged, while nasal CT 1 and CT 2 showed significant alterations. The reduction was confined to the nasal quadrant of the DCP and the entire RPC. This suggests that in PDS linked to elevated endogenous cortisol, pathological changes primarily manifest in the peripapillary region. We propose that the peripapillary region's unique anatomy makes it particularly vulnerable to high-dose endogenous cortisol, offering new insights into PDS initiation and progression.

The cross-sectional design of the study prevents conclusions about causality or disease progression. Second, although including only newly diagnosed, treatment-naive CD patients helped minimize confounding factors, the relatively small sample size, as well as the low number of patients in subgroups, limits the generalizability of our findings and highlights the need for larger, multicenter studies. Additionally, one limitation of our study is the low number of CD patients presenting with overt PDS features (except PPE), which limited our ability to perform direct comparisons with non-Cushing PDS patients.

This study presents the first quantitative analysis of retinochoroidal vascular changes in treatment-naive patients with CD. Our findings suggest that elevated endogenous cortisol primarily affects the peripapillary region and nasal macula, although the exact mechanisms remain unclear. Choroidal and peripapillary VD alterations appear to precede pachyvessel formation and choroidal thickening, with retinal plexus involvement occurring at a later stage. OCTA proves valuable in detecting early, subclinical microvascular changes, potentially before overt pachychoroid features or systemic complications manifest. These findings provide new insights into the systemic vascular impact of hypercortisolism in CD. Further large-scale studies are warranted to confirm and expand upon these results.

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