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Retinal microvasculature alteration in patients with acute pancreatitis: an observational OCTA study

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Abstract

Objective To evaluate changes in retinal layer thickness and microvascular density in pancreatitis patients using optical coherence tomography angiography (OCTA).

Methods The study involved 16 pancreatitis patients and 16 healthy controls. Each participant underwent a superficial OCTA scan, with images divided into nine subregions to compare macular retinal thickness (RT) and superficial vascular density (SVD) between groups.

Results Pancreatitis patients exhibited reduced retinal thickness in specific macular areas, including inner, full, and outer layers ($p < 0.05$). Additionally, decreased superficial vascular density was noted in inner superior (IS), outer superior (OS), inner nasal (IN), and outer nasal (ON) regions ($p < 0.05$). ROC curve analysis showed high diagnostic accuracy for full-layer inner superior, outer superior, and outer inferior thickness with areas under the curve of 0.9429, 0.9233, and 0.9990, respectively.

Conclusions Pancreatitis is associated with macular retinal thinning and decreased superficial vascular density, offering potential for improved diagnostic imaging.

Keywords Pancreatitis, Retinal thickness, Optical coherence tomography angiography (OCTA), Superficial vascular density, Macular region

Introduction

Acute pancreatitis is a pathological condition resulting from the inappropriate activation of pancreatic enzymes, leading to self-digestion. The annual global incidence of acute pancreatitis is reported to be 34 cases per 100,000 individuals, with no discernible disparity between genders [1]. This condition predominantly impacts individuals in the middle-aged and elderly demographic [2]. The combined annual mortality rate stemming from acute pancreatitis stands at 1.16 per 100,000 individuals [1, 2]. Despite a noticeable decline in case fatality rates associated with acute pancreatitis, the overall mortality rate attributed to acute pancreatitis within the population has remained constant [3, 4].

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Various factors contribute to the risk of mortality in cases of acute pancreatitis, such as persistent organ failure and infected pancreatic necrosis [5–7]. These are also serious complications of acute pancreatitis [8]. The incidence of acute pancreatitis is rising annually, particularly in Europe [9, 10]. Acute pancreatitis is increasingly becoming one of the most significant acute digestive system diseases in many parts of the world.

Acute pancreatitis typically presents with severe abdominal pain as its predominant symptom, frequently accompanied by nausea, vomiting, and feelings of bloating [11]. Severe cases of pancreatitis can result in serious complications such as shock, respiratory failure, and multiple organ dysfunction syndrome, posing a significant risk to patient survival [12].

The diagnosis of acute pancreatitis commonly entails confirmation through clinical manifestations, medical background, and pertinent laboratory evaluations. Standard assessments encompass blood analyses, ultrasonography, and imaging modalities like computed tomography (CT) scans [13, 14]. Given the vague presentation of initial symptoms of acute pancreatitis, pancreatic aspiration and histological examination may be necessary for additional validation of diagnosis in challenging cases and when differential diagnoses need to be considered [15]. The present diagnostic modalities exhibit constraints, with significant limiting factors encompassing test specificity and sensitivity, invasiveness level, patient condition-based restrictions, and examination cost.

Some research has been conducted on Purtscher's retinopathy as a rare ocular complication of acute pancreatitis [16]. However, recent studies indicate that in addition to Purtscher's retinopathy, other significant alterations in the fundus may be linked to pancreatitis [17]. Asymptomatic fundus changes such as cotton wool spots or retinal hemorrhages have been observed in cases of acute pancreatitis [17]. Patients without evident Purtscher's retinopathy have exhibited asymptomatic optic disc edema and retinal hemorrhages, particularly in cases of moderate-to-severe acute pancreatitis [17]. These findings present novel insights into the potential application of optical coherence tomography angiography (OCTA) for diagnosing pancreatitis. OCTA, a non-invasive imaging technology, offers direct in vivo visualization of ocular microvascular changes [18–20]. Various systemic diseases, including diabetes [21], primary hyperthyroidism [22], and cancer [23], are known to manifest ocular changes. OCTA enables visualization of the microvasculature of the macula and optic disc, aiding in the diagnosis of conditions such as Alzheimer's [24], diabetes [25, 26], and thyroid-related eye diseases [27, 28]. Optical Coherence Tomography (OCT) plays an important role as a non-invasive examination in the diagnosis of various diseases, including viral diseases [29, 30].

This study examines the ocular conditions of individuals diagnosed with pancreatitis, utilizing optical coherence tomography angiography (OCTA) to evaluate retinal thickness (RT) and vascular density (VD) in comparison to a control group of healthy individuals. The objective is to investigate the relationship between various examination indices, such as vision, and pancreatitis, with the goal of offering insights for the diagnosis and management of pancreatic diseases.

Methods

Participants

In 2023, a retrospective case–control study was carried out at the Department of Ophthalmology and Gastroenterology of the First Affiliated Hospital of Nanchang University in Nanchang, China. The study recruited participants with pancreatitis from the Department of Gastroenterology and healthy control subjects from the Clinical Research Center for Eye Diseases, with 16 individuals in each group. The participants were assessed for ocular abnormalities by an ophthalmologist from the medical center using clinical examination and OCTA imaging. All participants underwent evaluation by the same retinal specialist.

Recruitment criteria

Patients diagnosed with pancreatitis were required to adhere to the classification criteria outlined in the 2012 International Association of Pancreatology (IAP) published Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus [31], or the ACG Clinical Guideline: Chronic Pancreatitis published in 2020 [32]. All patients exhibited an absence of symptoms related to retinal vasculitis, choroiditis, or optic neuritis. Patients presenting with chorioretinal disorders attributed to hydroxychloroquine (HCQ) were specifically excluded from the study.

Exclusion conditions

Participants who meet any of the following criteria will be ineligible for inclusion in the study: (1) a history of ocular trauma or surgery; (2) systemic diseases impacting the eyes or optic nerve, such as hypertension (cardiovascular disease), diabetes (endocrine and metabolic disorder), or Alzheimer's disease (neurological disorder); (3) ocular diseases affecting the choroid or retina, such as choroiditis and age-related macular degeneration; (4) other conditions that could potentially impact fundus imaging; (5) pregnant or lactating individuals; (6) a history of alcohol or substance abuse.

Clinical examinations

All participants underwent the following clinical tests and ophthalmic examinations: (1) assessment of psychological state using the Hospital Anxiety and Depression Scale (HADS); (2) ocular measurements, including visual acuity (VA) (Snellen chart) and intraocular pressure (IOP) (Goldmann applanation tonometry); (3) optical coherence tomography angiography (OCTA).

OCTA

For OCTA imaging, the RTVue Avanti XR system (Optovue, Fremont, CA, USA) was utilized to visualize retinal cross-sectional views and microvasculature. The scanning speed was configured at 70,000 A-scans per second, with an axial resolution of 5 mm, a lateral resolution of 22 μm, a central wavelength of 840 nm, and a bandwidth of 45 nm. Angiography was conducted five times in a 6 mm x 6 mm scanning pattern using a B-scan (x-axis) to capture 216 raster locations (y-axis) centered on the macular region, with an acquisition time of 3.9 s. A total of 1,080 B-scans were captured at a frame rate of 270 frames per second, consisting of 216 y positions and 5 passes [33]. A 3 mm x 3 mm OCTA image was generated from four-volume scans, including 2 horizontal and 2 vertical rasters, totaling 933,120 A-scans. Subsequently, a 3 mm x 3 mm en face OCTA angiogram was computed for each eye. Utilizing the Early Treatment Diabetic Retinopathy Study (ETDRS) [34] method of dividing retinal subfields into three concentric circles with radii of 0.5 mm, 1.5 mm, and 3 mm, the retina was segmented into nine regions for thickness analysis. The study examined nine distinct retinal regions, encompassing inner nasal (IN), outer nasal (ON), inner inferior (II), outer inferior (OI), inner temporal (IT), outer temporal (OT), inner superior (IS), outer superior (OS), and the macular center (C). Retinal thickness (RT) was assessed from the internal limiting membrane (ILM) to the inner plexiform layer, with full RT measured from ILM to the retinal pigment epithelium (RPE). The disparity between these two measurements, full RT and inner RT, represents the outer RT. Vascular density was calculated by generating a model extending from the foveal center to the periphery of a 3 mm x 3 mm luminance gradient image, and assessing both macular retinal thickness and superficial vascular density (SVD). Data from the right eye were utilized for all participants, necessitating a mirroring of data from the left eye. Subsequently, the combined datasets were averaged and analyzed collectively.

Statistical analysis

The data were analyzed utilizing SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9.5 (GraphPad Software, La Jolla, CA, USA), with results presented as mean values ± standard deviations. Statistical comparisons between groups were conducted using independent sample t-tests and Chi-square tests. Pearson correlation analysis was employed to assess the relationship between various observational indicators. Receiver operating characteristic (ROC) curves were generated for RT (full, inner, outer) and SVD to compare healthy individuals with those diagnosed with pancreatitis, and the area under the curve (AUC) was calculated. Statistical significance was determined by a *P*-value of less than 0.05.

Results

General data analysis

There was no significant difference in the average age between the two cohorts, with the pancreatitis group having an average age of 50.33 ± 2.80 years, while the normal group had an average age of 49.83 ± 3.20 years ($P=0.747$). Similarly, no significant difference in gender distribution was noted, as the pancreatitis group consisted of 9 males and 7 females, while the normal group comprised 8 males and 8 females ($P=0.780$). Notably, both intraocular pressure and visual acuity were determined to be statistically significant ($P=0.017$; $P<0.001$, respectively) (Table 1).

Macular retinal thickness analysis

The retinal thickness data in each region for the inner, outer, and full layers conformed to a normal distribution for both study groups. In the control group, all macular regions—except for the C—showed significantly higher full-layer retinal thickness compared to the pancreatitis group, with statistically significant differences (IS: $P<0.001$; OS: $P<0.001$; IN: $P<0.001$; ON: $P<0.001$; II: $P<0.001$; OI: $P=0.005$; IT: $P<0.001$; OT: $P<0.001$); specifically, the IS, OS, IN, ON, and C regions showed significantly higher inner retinal thickness in the control group compared to the pancreatitis group (IS: $P<0.001$; OS: $P<0.001$; IN: $P<0.001$;

Table 1 General information of pancreatitis patients and healthy subjects

	Pancreatitis	HC	*t*	*P*
Gender (male/female)	9/7	8/8	–	0.780
Age (years)	56.31 ± 5.78	49.81 ± 5.80	3.175	**0.003**
Intraocular pressure (mmHg)	14.31 ± 1.45	15.30 ± 1.76	− 2.444	**0.017**
Visual acuity (LogMAR)	0.60 ± 0.18	0.90 ± 0.13	− 7.614	**< 0.001**

Bold values indicate $P<0.05$. Gender analysis used the Chi-square test; comparisons of age, intraocular pressure, and visual acuity were performed using independent sample *t*-tests. *HC* healthy control

ON: $P<0.001$; C: $P=0.029$), while the II, OI, IT, and OT showed no statistically significant differences ($P>0.05$); for the outer layer, all regions except for the C—which showed no statistically significant difference ($P>0.05$)—were thicker in the control group compared to the pancreatitis group (IS: $P<0.001$; OS: $P<0.001$; IN: $P<0.001$; ON: $P<0.001$; II: $P=0.009$; OI: $P=0.010$; IT: $P<0.001$; OT: $P<0.001$) (Table 2).

Table 2 Comparison of macular retinal thickness at different locations between pancreatitis patients and healthy subjects

Location	Pancreatitis ($n=16$, 32 eyes)	HC ($n=16$, 32 eyes)	*t*	*P*
Macular full retinal thickness (μm, mean ± SD)				
IS	291.91 ± 22.37	333.06 ± 14.29	− 8.770	**< 0.001**
OS	267.34 ± 15.38	299.22 ± 20.80	− 6.969	**< 0.001**
IN	302.38 ± 19.08	330.06 ± 14.78	− 6.490	**< 0.001**
ON	282.81 ± 15.23	317.88 ± 7.93	− 11.553	**< 0.001**
II	308.00 ± 20.55	324.44 ± 14.81	− 3.671	**< 0.001**
OI	268.13 ± 22.11	280.44 ± 6.41	− 3.025	**0.005**
IT	294.81 ± 24.40	316.50 ± 13.80	− 4.377	**< 0.001**
OT	257.50 ± 15.07	275.38 ± 6.82	− 6.113	**< 0.001**
C	236.44 ± 25.49	244.19 ± 30.23	− 1.109	0.272
Macular inner retinal thickness (μm, mean ± SD)				
IS	103.13 ± 13.26	113.13 ± 5.85	− 3.903	**< 0.001**
OS	100.28 ± 9.63	110.28 ± 6.16	− 4.950	**< 0.001**
IN	107.56 ± 10.34	115.78 ± 5.84	− 3.915	**< 0.001**
ON	113.09 ± 9.61	123.47 ± 4.34	− 5.568	**< 0.001**
II	113.09 ± 13.29	114.22 ± 5.22	− 0.446	0.658
OI	102.75 ± 10.40	104.09 ± 6.23	− 0.627	0.533
IT	103.53 ± 8.18	104.91 ± 3.51	− 0.874	0.387
OT	94.25 ± 5.16	94.31 ± 5.50	− 0.047	0.963
C	49.56 ± 5.42	52.53 ± 5.22	− 2.231	**0.029**
Macular outer retinal thickness (μm, mean ± SD)				
IS	188.78 ± 26.60	219.94 ± 15.07	− 5.764	**< 0.001**
OS	167.06 ± 15.44	188.93 ± 21.90	− 4.619	**< 0.001**
IN	194.81 ± 21.34	214.28 ± 14.24	− 4.292	**< 0.001**
ON	169.72 ± 19.34	194.41 ± 9.09	− 6.536	**< 0.001**
II	194.91 ± 27.23	210.22 ± 16.42	− 2.724	**0.009**
OI	165.38 ± 21.52	176.34 ± 7.94	− 2.705	**0.010**
IT	191.28 ± 26.78	211.59 ± 14.82	− 3.754	**< 0.001**
OT	163.25 ± 15.31	181.06 ± 8.39	− 5.771	**< 0.001**
C	186.88 ± 24.95	191.66 ± 30.79	− 0.682	0.498

Bold values indicate $P<0.05$. The *P*-values comparing the internal, external, and complete macular retinal thicknesses between pancreatitis patients and healthy subjects were obtained using independent sample *t*-tests. *HC* healthy control, *IS* inner superior, *OS* outer superior, *IN* inner nasal, *ON* outer nasal, *II* inner inferior, *OI* outer inferior, *IT* inner temporal, *OT* outer temporal, *C* central

Analysis of superficial vascular density in the macular region

The retinal vascular density in the IS, OS, IN, ON, IT, and C regions of the control group was significantly greater compared to the pancreatitis group, with statistically significant variations between the two groups ($P<0.001$; $P<0.001$; $P<0.001$; $P<0.001$; $P=0.001$; $P=0.004$, respectively). Conversely, no significant differences were observed in the remaining regions ($P>0.05$) (Table 3, Fig. 1).

Analysis of receiver operating characteristic curves for full-layer, inner-layer, outer-layer retinal thickness, and superficial vessel density

ROC curve analysis was conducted on the full-layer, inner-layer, and outer-layer retinal regions, revealing statistically significant differences between the two groups. The AUC was utilized to assess the sensitivity and specificity of diagnosis. The AUCs of retinal thickness in the full-layer regions of IS, OS, IN, ON, II, OI, IT, and OT were 0.9429 (95%CI: 0.8892 to 0.9965), 0.9233 (95%CI: 0.8524 to 0.9943), 0.8604 (95%CI: 0.7728 to 0.9479), 0.9990 (95%CI: 0.9958 to 1.000), 0.7388 (95%CI: 0.6157 to 0.8618), 0.7061 (95%CI: 0.5654 to 0.8467), 0.7925 (95%CI: 0.6827 to 0.9023), and 0.8545 (95%CI: 0.7543 to 0.9547), respectively. IS, OS, and OI demonstrated very high diagnostic sensitivity for pancreatitis, while IN showed relatively high diagnostic sensitivity.

Significant differences in inner-layer thickness were observed in the regions IS, OS, IN, ON, and C between the two groups, with corresponding AUC values of 0.7065 (95%CI: 0.5683 to 0.8448), 0.7959 (95%CI: 0.6793 to 0.9125), 0.7100 (95%CI: 0.5747 to 0.8453),

Table 3 Comparison of superficial vessel density at different locations between pancreatitis patients and healthy subjects

Location	Pancreatitis ($n=16$, 32 eyes)	HC ($n=16$, 32 eyes)	*t*	*P*
IS	45.63 ± 6.40	53.81 ± 3.57	− 6.321	< 0.001
OS	43.34 ± 6.48	51.53 ± 2.82	− 6.556	< 0.001
IN	45.81 ± 4.15	51.09 ± 3.65	− 5.404	< 0.001
ON	49.63 ± 4.38	53.88 ± 2.76	− 4.643	< 0.001
II	51.78 ± 9.28	52.88 ± 3.70	− 0.620	0.539
OI	51.66 ± 5.49	52.56 ± 2.82	− 0.831	0.410
IT	51.16 ± 4.60	54.47 ± 2.90	− 3.447	0.001
OT	48.91 ± 4.35	50.75 ± 3.02	− 1.970	0.053
C	21.94 ± 3.73	24.84 ± 4.10	− 2.963	0.004

Bold values indicate $P<0.05$. *P*-values comparing superficial vessel density between pancreatitis patients and healthy subjects were obtained using independent sample *t*-tests. *HC* healthy control, *IS* inner superior, *OS* outer superior, *IN* inner nasal, *ON* outer nasal, *II* inner inferior, *OI* outer inferior, *IT* inner temporal, *OT* outer temporal, *C* central

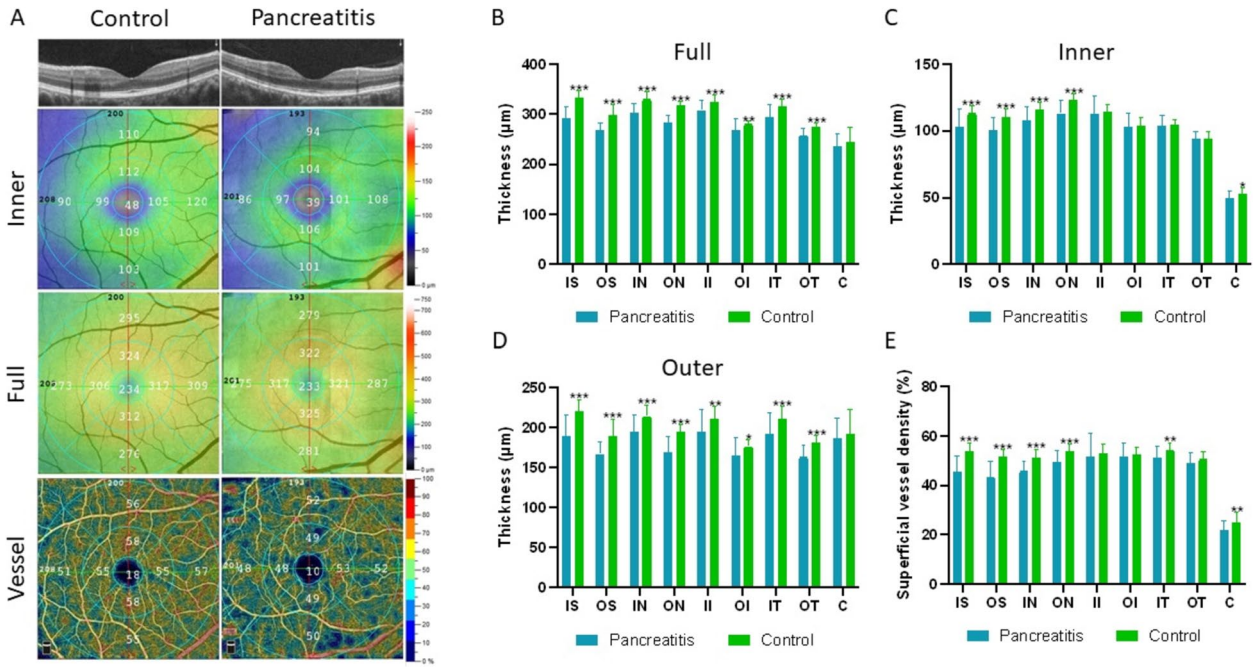

Fig. 1 OCTA images and analysis of RT and SVD for control and pancreatitis groups. A Cross-sectional images of RT using OCTA for the control and pancreatitis groups. Inner RT, full RT, and SVD were measured by ETDRS. B-D Analysis of RT results for the pancreatitis and healthy groups. The ordinate is the value of RT, and the abscissa is the sub-region of the retina. E Analysis of SVD results for the pancreatitis and healthy groups. The ordinate is the value of SVD, and the abscissa is the sub-region of the retina. *OCTA* optical coherence tomography angiography, *RT* retinal thickness, *SVD* superficial vessel density, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IS* inner superior, *OS* outer superior, *IN* inner nasal, *ON* outer nasal, *II* inner inferior, *OI* outer inferior, *IT* inner temporal, *OT* outer temporal, *C* central. * $P<0.05$; ** $P<0.01$; *** $P<0.001$

0.8296 (95%CI: 0.7177 to 0.9415), and 0.6948 (95%CI: 0.5652 to 0.8244), respectively. Notably, the ON region exhibited higher diagnostic sensitivity in terms of inner-layer thickness.

The outer-layer thickness of the regions IS, OS, IN, ON, II, OI, IT, and OT in the control group exhibited significantly greater thickness compared to the pancreatitis group, as evidenced by the respective AUC values of 0.8369 (95%CI: 0.7353 to 0.9386), 0.8101 (95%CI: 0.7043 to 0.9158), 0.7617 (95%CI: 0.6443 to 0.8791), 0.8828 (95%CI: 0.8033 to 0.9623), 0.6865 (95%CI: 0.5520 to 0.8211 twice), 0.7417 (95%CI: 0.6194 to 0.8640), and 0.8413 (95%CI: 0.7412 to 0.9414), respectively. Notably, IS, OS, ON, and OT regions demonstrated high diagnostic sensitivity.

The superficial vessel density of the retina in various regions (IS, OS, IN, ON, IT, and C) was estimated using ROC curve analysis, resulting in area under the curve (AUC) values of 0.8979 (95%CI: 0.8135 to 0.9824), 0.8467 (95%CI: 0.7432 to 0.9502), 0.8457 (95%CI: 0.7426 to 0.9488), 0.7749 (95%CI: 0.6592 to 0.8906), 0.7139 (95%CI: 0.5853 to 0.8424), and 0.6924 (95%CI: 0.5630 to 0.8218), respectively. IS, OS, and IN regions exhibited higher diagnostic sensitivity (Fig. 2).

Correlation between retinal thickness, vascular density, and intraocular pressure in the pancreatitis group

Upon examination of the relationship between retinal superficial vascular density, retinal thickness, and intraocular pressure, it was determined that among individuals with pancreatitis, only the superficial vascular density in the IN region exhibited a statistically significant correlation with intraocular pressure ($P=0.031$), demonstrating a negative correlation ($r=-0.382$) (Table 4).

The correlation between retinal thickness, vascular density, and visual acuity in the pancreatitis group

After conducting an analysis of the relationship between retinal superficial vascular density, retinal thickness, and visual acuity, it was observed that within the pancreatitis group, a positive correlation existed between superficial blood vessels in the IS region of the retina and the thickness of the outer retinal OS region with visual acuity. Conversely, a negative correlation was observed between the thickness of the inner retinal OS region and visual acuity. No statistically significant correlations were identified between retinal superficial vascular density or retinal thickness in other regions and visual acuity ($P>0.05$) (Table 5, Fig. 3).

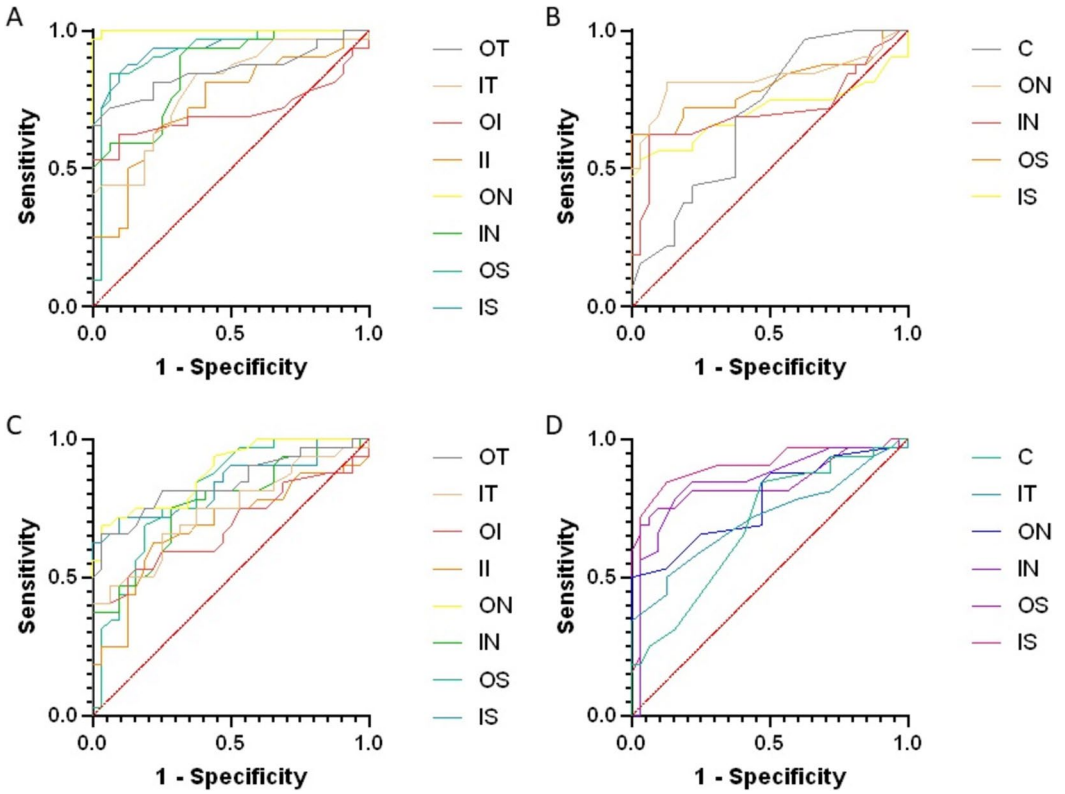

Fig. 2 Receiver operating characteristic (ROC) curve analysis for RT and SVD. **A** Area under the ROC curve for full-layer IS, OS, IN, ON, II, OI, IT, OT are 0.9429 (95%CI: 0.8892 to 0.9965), 0.9233 (95%CI: 0.8524 to 0.9943), 0.8604 (95%CI: 0.7728 to 0.9479), 0.9990 (95%CI: 0.9958 to 1.000), 0.7388 (95%CI: 0.6157 to 0.8618), 0.7061 (95%CI: 0.5654 to 0.8467), 0.7925 (95%CI: 0.6827 to 0.9023), 0.8545 (95%CI: 0.7543 to 0.9547), respectively. **B** The AUC for the inner layers IS, OS, IN, ON, C are 0.7065 (95%CI: 0.5683 to 0.8448), 0.7959 (95%CI: 0.6793 to 0.9125), 0.7100 (95%CI: 0.5747 to 0.8453), 0.8296 (95%CI: 0.7177 to 0.9415), 0.6948

Table 4 Correlation analysis of retinal thickness, superficial vascular density, and visual acuity in different regions of patients with pancreatitis

	Visual acuity	
	r	*P*
Superficial vascular density in the IS region	0.550	0.001
Inner retinal thickness in the OS region	− 0.405	0.021
Outer retinal thickness in the OS region	0.481	0.005

The *P*-values for retinal thickness, superficial vascular density, and visual acuity were obtained through Pearson analysis. All *P*-values are less than 0.05. *IS* inner superior, *OS* outer superior

Table 5 Correlation analysis of retinal thickness and superficial vascular density in different regions between patients with pancreatitis and healthy subjects

	Superficial vascular density of the retina	
	r	*P*
Pancreatitis		
Outer retinal thickness in the ON region	− 0.364	0.041
Inner retinal thickness in the II region	− 0.375	0.034
HC		
Full retinal thickness in the IS region	− 0.394	0.026
Full retinal thickness in the OS region	− 0.624	< 0.001
Outer retinal thickness in the OS region	− 0.566	< 0.001

P-values for the correlation between retinal thickness and superficial vascular density were obtained through Pearson analysis. All *P*-values were less than 0.05. *HC* healthy control, *IS* inner superior, *OS* outer superior, *ON* outer nasal, *II* inner inferior

Correlation between retinal superficial vascular density and retinal thickness

The study utilized Pearson analysis to examine the relationship between retinal superficial vascular density and retinal thickness. Results indicated a negative correlation between outer retinal thickness in the ON region and inner retinal thickness in the II region with superficial vascular density in the pancreatitis group ($P=0.041$; $P=0.034$), while no significant correlation was observed in other regions ($P>0.05$). In the control group, significant negative correlations were observed between

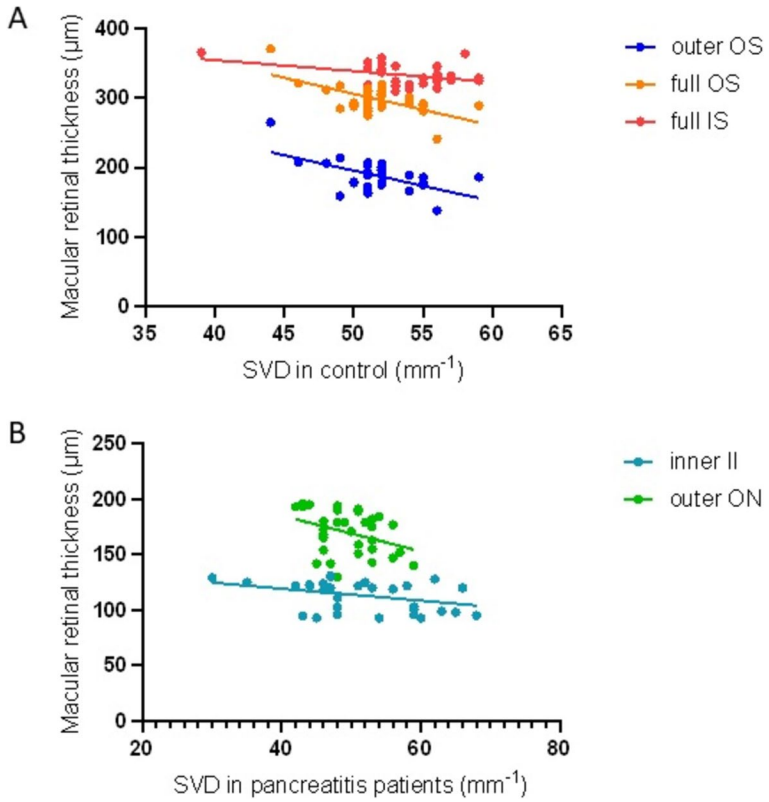

Fig. 3 Correlation between retinal thickness and SVD. A In the healthy control group, the full-layer retinal thickness in the IS region, the full-layer retinal thickness in the OS region, and the outer retinal thickness in the OS region were negatively correlated with the superficial retinal vascular density ($r = -0.394$, $P = 0.026$; $r = -0.624$, $P < 0.001$; $r = -0.566$, $P < 0.001$). B In the pancreatitis group, the outer retinal thickness in the ON region and the inner retinal thickness in the II region were negatively correlated with the superficial vascular density of the retina ($r = -0.364$, $P = 0.041$; $r = -0.375$, $P = 0.034$). *SVD* superficial vascular density, *IS* inner superior, *OS* outer superior, *ON* outer nasal, *II* inner inferior

superficial retinal vascular density and the full-layer retinal thickness in the IS region ($P = 0.026$), the full-layer retinal thickness in the OS region ($P < 0.001$), and the outer retinal thickness in the OS region ($P < 0.001$). No statistically significant correlations were found in the other regions ($P > 0.05$).

Discussion

Pancreatitis is a common gastrointestinal disorder that can impact pancreatic function and potentially contribute to pathophysiological alterations in various bodily systems [35]. Recent research suggests that systemic illnesses may influence the morphology and function of the retinal microvasculature. In recent years, an increasing number of studies have demonstrated the significant advantages of OCTA in the early detection of microvascular changes associated with systemic diseases [36, 37]. Therefore, OCTA plays an essential role in assessing retinal microvascular and structural changes in pancreatitis patients. The macular region serves as the primary locus for visual acuity, with alterations in retinal thickness and vascular density directly influencing visual function [38]. Despite this, the existing body of literature regarding changes in macular retinal structure and microvascular density in individuals with pancreatitis is characterized by inconsistencies, indicating a lack of comprehensive understanding in this area. This study employed OCTA technology to systematically observe and analyze the macular retinal thickness and superficial microvascular density in patients with pancreatitis, with the goal of enhancing our comprehension of the relationship between pancreatitis and the retinal microenvironment and investigating its potential clinical implications. Through a comparative analysis of patients with pancreatitis and a healthy control group, this study aims to contribute additional pathological evidence supporting the association between pancreatitis and retinal lesions, as well as propose novel insights for clinical diagnosis and treatment strategies.

In this study, retinal thickness was quantified utilizing the ETDRS segmentation method. Our analysis revealed a statistically significant reduction in retinal thickness among individuals with pancreatitis. This observation implies a potential association between pancreatitis

and structural abnormalities or damage within the retina. Given the neural nature of retinal tissue, it is known to be particularly susceptible to the effects of systemic diseases [39, 40]. Pancreatitis induces systemic vascular alterations [41], with severe acute pancreatitis potentially leading to both pancreatic and systemic microcirculatory disturbances via various mechanisms, including ischemia–reperfusion injury, vascular and perfusion abnormalities, oxidative stress, microvascular injury, and hemodynamic dysfunction characterized by vasoconstriction, inadequate perfusion, and heightened blood viscosity and coagulability [42, 43]. Retinal thinning may result from vascular changes within the retina, which can lead to compromised local blood circulation and inadequate nutrient delivery. Additionally, retinal thinning may be attributed to the influence of inflammatory factors on retinal neurons and support cells, either directly or indirectly. In a research investigation of Alzheimer's disease, heightened concentrations of pro-inflammatory cytokines, such as tumor necrosis factor, interleukin 1β, interleukin 6, and interferon γ, were identified. It was suggested that cytokine-induced neurotoxicity may exacerbate cellular apoptosis, resulting in neuronal demise [44]. Previous studies have investigated the effects of cytokines on the retina. The research found that cytokine-activated microglia release cytotoxins, leading to the death of retinal neurons [45]. Active interleukin 1β causes the gradual death of photoreceptor cells by initiating and propagating sterile inflammation, and it can also lead to chronic retinal degenerative changes through excessive inflammation, ultimately resulting in the apoptosis of retinal neurons [46]. In the retina, tumor necrosis factor and interleukin 1β trigger exogenous apoptotic pathways and the NLRP3 inflammasome pathway by binding to the receptors tumor necrosis factor receptor 1 and P2X7 receptor, leading to the death of retinal ganglion cells. These studies indicate that cytokines can affect the survival of retinal neurons through multiple pathways [47]. These findings suggest that the pro-inflammatory agents generated by pancreatitis could potentially induce neuronal impairment and cellular demise, consequently diminishing retinal thickness (Fig. 4).

The observed reduction in superficial retinal vascular density among patients with pancreatitis represents a significant discovery in our research. This decline in vascular density may suggest endothelial injury or compromised blood flow. Inflammatory cytokines generated as a result of the inflammatory process can lead to vascular abnormalities, subsequently impacting retinal blood flow [42, 43]. Given the systemic nature of pancreatitis-induced inflammation, these inflammatory mediators have the potential to affect various organs, including the eyes, through the circulatory system. Vascular inflammation is characterized by intricate interactions among inflammatory cells, endothelial cells, vascular smooth muscle cells, and the extracellular matrix [48, 49]. Cytokines are pivotal in orchestrating this process by initiating signaling cascades that culminate in inflammation, cellular adhesion, permeability, and apoptosis [50–52]. Cytokines, including tumor necrosis factor-alpha and interleukin-6, have been shown to induce the synthesis of endothelin-1 in vascular smooth muscle cells, resulting in endothelial dysfunction and subsequent vasoconstriction, potentially impacting retinal vascular density [53–55]. Furthermore, hemodynamic disturbances associated with pancreatitis may further exacerbate the reduction in retinal vascular density by affecting retinal blood flow [42, 43]. The reduction in superficial vascular density of the retina indicates a potential inadequacy in retinal blood supply, thereby heightening the vulnerability of neural tissues to damage, in alignment with the aforementioned findings on retinal thickness.

The reduction in retinal thickness and superficial vascular density may be attributed to diabetes secondary to pancreatitis. Wang et al. conducted a study which revealed a decrease in peripapillary vascular density in

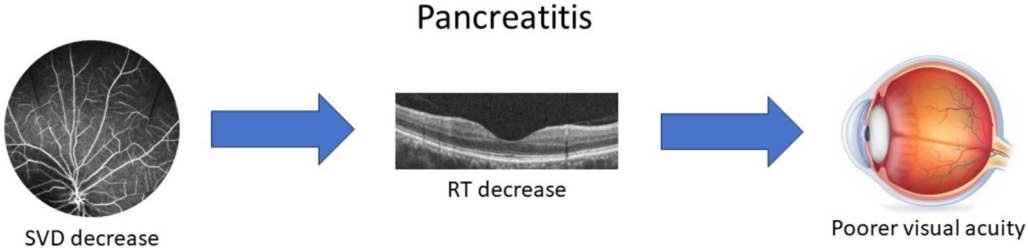

Fig. 4 The relationship between the reduction in superficial vascular density (SVD), the thinning of retinal thickness (RT), and the impairment of visual acuity in patients with pancreatitis. In patients with pancreatitis, a decrease in superficial retinal vascular density in the macular region may lead to a reduction in retinal thickness in the related areas, and a reduction in retinal thickness in the macular region may result in a decline in visual acuity. *RT* retinal thickness, *SVD* superficial vascular density

patients with mild-to-moderate nonproliferative diabetic retinopathy (NPDR) compared to healthy individuals. Furthermore, the study demonstrated a significant reduction in peripapillary capillary vascular density and retinal nerve fiber layer thickness in the superotemporal quadrant of the mild-to-moderate NPDR group [56]. A study conducted by Mokrane et al. demonstrated a positive correlation between subfoveal sensitivity of the superficial capillary plexus and vascular density [57] in patients with diabetic retinopathy. These results indicate that diabetes may induce structural and vascular alterations in the superficial retinal layers, aligning with the conclusions of our own research on pancreatitis.

The utilization of ROC curve analysis serves as a valuable method for evaluating the precision of diagnostic tests, allowing for the assessment of specific biomarkers in distinguishing between healthy individuals and those afflicted with disease. The examination of ROC curves pertaining to the full-layer inner superior, outer superior, and outer inferior thicknesses may present a viable approach for the diagnosis of pancreatitis. Timely diagnosis and precise evaluation play a pivotal role in the effective management and positive outcomes of pancreatitis [58, 59]. Nevertheless, early detection of pancreatitis poses a challenge due to the nonspecific nature of initial symptoms. Symptoms commonly associated with acute pancreatitis, such as upper abdominal pain, abdominal distension, nausea, and vomiting, are also characteristic of numerous other gastrointestinal disorders. The challenge of early diagnosis in chronic pancreatitis is compounded by the gradual onset and progression of symptoms over an extended period. OCTA offers a non-invasive and convenient method for assessing perfusion in the intraocular vascular network, with retinal thickness potentially serving as a valuable biomarker for aiding in the diagnosis of pancreatitis. Currently, this discovery is being investigated as a potential avenue for future research to confirm its validity, with the potential to serve as a novel method for detecting and monitoring pancreatitis.

In summary, pancreatitis exerts a notable influence on retinal structure, presenting a novel angle for the supplementary diagnosis of pancreatitis. It is important to highlight that while our results hold promise for clinical utility, extensive prospective investigations are required to ascertain the sensitivity, specificity, and prognostic significance of alterations in retinal parameters. Furthermore, due to the small sample size of this study, further investigation is warranted to expand the sample size in order to elucidate the specific relationship between these retinal alterations and the pathophysiology of pancreatitis, as well as their potential correlation with disease severity and progression. Subsequent research efforts should also prioritize the strategic utilization of these retinal changes in order to develop individualized diagnostic and therapeutic strategies for patients.

Conclusion

Optical coherence tomography angiography (OCTA) was employed in our study to evaluate the effects of retinal thickness (RT) and superficial vascular density (SVD) in individuals with pancreatitis. Our findings revealed that patients with pancreatitis exhibited decreased retinal thickness and superficial vascular density in specific areas of the macular region when compared to the control group. Consequently, the identification of imaging changes through OCTA may serve as a valuable adjunctive method for the diagnosis and evaluation of pancreatitis.

Author contributions

X.-Z.Q.: Writing—original draft, Writing—review and editing. J.Y.H.: Conceptualization, Resources, Writing—review and editing. Y.-M.Z.: Resources, Data curation, Writing—review and editing. H.W.: Data curation, Writing—review and editing. X.-Y.W.: Resources, Data curation, Writing—review and editing. C.C.: Validation, Writing—review and editing. Q.M.G.: Writing—review and editing. J.Z.: Conceptualization, Writing—review and editing. X.M.Z.: Resources, Writing—review and editing. Q.L.: Writing—original draft, Writing—review and editing. L.Q.H.: Writing—review and editing. X.L.: Writing—review and editing. Y.S.: Conceptualization, Resources, Project administration, Writing—review and editing.

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Data availability

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the First Affiliated Hospital of Nanchang University and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Competing interests

The authors declare no competing interests.

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References

1. Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies.

Lancet Gastroenterol Hepatol. 2016;1(1):45–55. https://doi.org/10.1016/s2468-1253(16)30004-8.
2. Pendharkar SA, Mathew J, Petrov MS. Age- and sex-specific prevalence of diabetes associated with diseases of the exocrine pancreas: A population-based study. Dig Liver Dis. 2017;49(5):540–4. https://doi.org/10.1016/j.dld.2016.12.010.
3. Munigala S, Yadav D. Case-fatality from acute pancreatitis is decreasing but its population mortality shows little change. Pancreatology. 2016;16(4):542–50. https://doi.org/10.1016/j.pan.2016.04.008.
4. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas. 2006;33(4):323–30. https://doi.org/10.1097/01.mpa.0000236733.31617.52.
5. Frey C, Zhou H, Harvey D, White RH. Co-morbidity is a strong predictor of early death and multi-organ system failure among patients with acute pancreatitis. J Gastrointest Surg. 2007;11(6):733–42. https://doi.org/10.1007/s11605-007-0164-5.
6. Hong S, Qiwen B, Ying J, Wei A, Chaoyang T. Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. Eur J Gastroenterol Hepatol. 2011;23(12):1136–43. https://doi.org/10.1097/MEG.0b013e32834b0e0e.
7. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology. 2010;139(3):813–20. https://doi.org/10.1053/j.gastro.2010.06.010.
8. Garg PK, Singh VP. Organ failure due to systemic injury in acute pancreatitis. Gastroenterology. 2019;156(7):2008–23. https://doi.org/10.1053/j.gastro.2018.12.041.
9. Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. Gastroenterology. 2022;162(1):122–34. https://doi.org/10.1053/j.gastro.2021.09.043.
10. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017;17(2):155–65. https://doi.org/10.1016/j.pan.2017.01.005.
11. Beiriger J, Khan A, Yan B, Ross H, Wang M, Carducci M, et al. Comprehensive review of acute pancreatitis pain syndrome. Gastrointest Disord. 2023;5(2):144–66. https://doi.org/10.3390/gidisord5020014.
12. Nohomovich B, Shah A, Hughes N. Severe, complicated pancreatitis with an unclear etiology. Cureus. 2023;15(5): e39011. https://doi.org/10.7759/cureus.39011.
13. Aliyeva GR. Diagnostic value of research methods in diagnostics of chronic pancreatitis. Kazan Med J. 2021;102(4):528–36. https://doi.org/10.17816/kmj2021-528.
14. Basnayake C, Ratnam D. Blood tests for acute pancreatitis. Aust Prescr. 2015;38(4):128–30. https://doi.org/10.18773/austprescr.2015.043.
15. Thompson BS, Philcox S, Devereaux B, Metz AJ, Croagh D, Gray A, et al. Prodromal signs and symptoms of chronic pancreatitis: a systematic review. J Clin Gastroenterol. 2022;56(1):e1–10. https://doi.org/10.1097/MCG.0000000000001544.
16. Yadlapalli NM, Abdulwahid T, Musgrove C, Afzal R, Francis F, Waxman E. S1815 ° Purtscher retinopathy: a rare clinical manifestation of acute pancreatitis. Am J Gastroenterol. 2022. https://doi.org/10.14309/01.ajg.0000863900.98267.6e.
17. Pandey R, Rana SS, Gupta V, Agarwal A, Kang M, Sharma RK, et al. Retinochoroidal changes in patients with acute pancreatitis: a prospective analysis of a novel biomarker. Pancreatology. 2020;20(8):1604–10. https://doi.org/10.1016/j.pan.2020.10.037.
18. Ghasemi Falavarjani K, Tian JJ, Akil H, Garcia GA, Sadda SR, Sadun AA. Swept-source optical coherence tomography angiography of the optic disk in optic neuropathy. Retina. 2016;36(Suppl 1):S168–77. https://doi.org/10.1097/iae.0000000000001259.
19. Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers in macular telangiectasia type 2 imaged by optical coherence tomographic angiography. JAMA Ophthalmol. 2015;133(1):66–73. https://doi.org/10.1001/jamaophthalmol.2014.3950.
20. Wu H, Sekiryu T, Sugano Y, Itagaki K, Kasai A, Shintake H. A modified measuring method to investigate the choriocapillaris flow void of polypoidal choroidal vasculopathy with swept source optical coherence tomography angiography. Quant Imaging Med Surg. 2021;11(7):3146–56. https://doi.org/10.21037/qims-20-1027.
21. Yu Y, Lan DY, Tang LY, Su T, Li B, Jiang N, et al. Intrinsic functional connectivity alterations of the primary visual cortex in patients with proliferative diabetic retinopathy: a seed-based resting-state fMRI study. Ther Adv Endocrinol Metab. 2020;11:2042018820960296. https://doi.org/10.1177/2042018820960296.
22. Liu WF, Shu YQ, Zhu PW, Li B, Shi WQ, Lin Q, et al. The cerebellum posterior lobe associates with the exophthalmos of primary hyperthyroidism: a resting-state fMRI study. Int J Endocrinol. 2019;2019:8135671. https://doi.org/10.1155/2019/8135671.
23. Liu JX, Yuan Q, Min YL, He Y, Xu QH, Li B, et al. Apolipoprotein A1 and B as risk factors for development of intraocular metastasis in patients with breast cancer. Cancer Manag Res. 2019;11:2881–8. https://doi.org/10.2147/cmar.S191352.
24. Cunha JP, Proença R, Dias-Santos A, Almeida R, Águas H, Alves M, et al. OCT in Alzheimer's disease: thinning of the RNFL and superior hemiretina. Graefes Arch Clin Exp Ophthalmol. 2017;255(9):1827–35. https://doi.org/10.1007/s00417-017-3715-9.
25. Hasegawa N, Nozaki M, Takase N, Yoshida M, Ogura Y. New insights into microaneurysms in the deep capillary plexus detected by optical coherence tomography angiography in diabetic macular edema. Invest Ophthalmol Vis Sci. 2016;57(9):348–55. https://doi.org/10.1167/iovs.15-18782.
26. Wang Y, Shao Y, Shi WQ, Jiang L, Wang XY, Zhu PW, et al. The predictive potential of altered spontaneous brain activity patterns in diabetic retinopathy and nephropathy. EPMA J. 2019;10(3):249–59. https://doi.org/10.1007/s13167-019-00171-4.
27. Lai FHP, Iao TWU, Ng DSC, Young AL, Leung J, Au A, et al. Choroidal thickness in thyroid-associated orbitopathy. Clin Exp Ophthalmol. 2019;47(7):918–24. https://doi.org/10.1111/ceo.13525.
28. Jiang YP, Yang YC, Tang LY, Ge QM, Shi WQ, Su T, et al. Altered spontaneous brain activity patterns in dysthyroid optic neuropathy: a resting-state fMRI study. J Integr Neurosci. 2021;20(2):375–83. https://doi.org/10.31083/j.jin2002037.
29. Kal M, Brzdęk M, Winiarczyk M, Mackiewicz J, Kozieł D, Odrobina D, et al. Retinal thickness in patients with elevated D-dimer and interleukin-6 levels as a result of SARS-CoV-2 infection. Med Stud/Studia Medyczne. 2023;39(4):342–51. https://doi.org/10.5114/ms.2023.134085.
30. Kal M, Brzdęk M, Zarębska-Michaluk D, Pinna A, Mackiewicz J, Odrobina D, et al. Optical coherence tomography angiography assessment of the optic nerve head in patients hospitalized due to COVID-19 bilateral pneumonia. Medicina (Kaunas). 2024. https://doi.org/10.3390/medicina60030502.
31. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102–11. https://doi.org/10.1136/gutjnl-2012-302779.
32. Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG clinical guideline: chronic pancreatitis. Am J Gastroenterol. 2020;115(3):322–39. https://doi.org/10.14309/ajg.0000000000000535.
33. Kashani AH, Chen CL, Gahm JK, Zheng F, Richter GM, Rosenfeld PJ, et al. Optical coherence tomography angiography: a comprehensive review of current methods and clinical applications. Prog Retin Eye Res. 2017;60:66–100. https://doi.org/10.1016/j.preteyeres.2017.07.002.
34. Relhan N, Flynn HW Jr. The Early Treatment Diabetic Retinopathy Study historical review and relevance to today's management of diabetic macular edema. Curr Opin Ophthalmol. 2017;28(3):205–12. https://doi.org/10.1097/icu.0000000000000362.
35. SantosSomera L, DafneSherlynMoreno S, JonathanMoreno S. Management of hemorrhagic pancreatitis: review of the current literature. Int J Med Sci Clin Res Stud. 2023;3(3):312–5. https://doi.org/10.47191/ijmscrs/v3-i3-07.
36. Rinaldi M, Chiosi F, Passaro ML, Natale F, Riccardo A, D'Andrea L, et al. Resistive index of central retinal artery, aortic arterial stiffness and OCTA correlated parameters in the early stage of Fabry disease. Sci Rep. 2024;14(1):24047. https://doi.org/10.1038/s41598-024-74146-5.
37. Chiosi F, Campagna G, Rinaldi M, Manzi G, dell'Omo R, Fiorentino G, et al. Optical coherence tomography angiography analysis of vessel density indices in early post-COVID-19 patients. Front Med (Lausanne). 2022;9:927121. https://doi.org/10.3389/fmed.2022.927121.
38. Živković MLJ, Lazić L, Zlatanovic M, Zlatanović N, Brzaković M, Jovanović M, et al. The influence of myopia on the foveal avascular zone and density

of blood vessels of the Macula-An OCTA Study. Medicina (Kaunas). 2023;59(3):452. https://doi.org/10.3390/medicina59030452.
39. Takayama K, Kaneko H, Ito Y, Kataoka K, Iwase T, Yasuma T, et al. novel classification of early-stage systemic hypertensive changes in human retina based on OCTA measurement of Choriocapillaris. Sci Rep. 2018;8(1):15163. https://doi.org/10.1038/s41598-018-33580-y.
40. Monteiro-Henriques I, Rocha-Sousa A, Barbosa-Breda J. Optical coherence tomography angiography changes in cardiovascular systemic diseases and risk factors: a review. Acta Ophthalmol. 2022;100(1):e1–15. https://doi.org/10.1111/aos.14851.
41. Komara NL, Paragomi P, Greer PJ, Wilson AS, Breze C, Papachristou GI, et al. Severe acute pancreatitis: capillary permeability model linking systemic inflammation to multiorgan failure. Am J Physiol Gastrointest Liver Physiol. 2020;319(5):G573–83. https://doi.org/10.1152/ajpgi.00285.2020.
42. Gomes CA, Di Saverio S, Sartelli M, Segallini E, Cilloni N, Pezzilli R, et al. Severe acute pancreatitis: eight fundamental steps revised according to the "PANCREAS" acronym. Ann R Coll Surg Engl. 2020;102(8):555–9. https://doi.org/10.1308/rcsann.2020.0029.
43. Foitzik T, Eibl G, Hotz B, Hotz H, Kahrau S, Kasten C, et al. Persistent multiple organ microcirculatory disorders in severe acute pancreatitis: experimental findings and clinical implications. Dig Dis Sci. 2002;47(1):130–8. https://doi.org/10.1023/a:1013284008219.
44. Rosenberg PB. Clinical aspects of inflammation in Alzheimer's disease. Int Rev Psychiatry. 2005;17(6):503–14. https://doi.org/10.1080/02646830500382037.
45. Krady JK, Basu A, Allen CM, Xu Y, LaNoue KF, Gardner TW, et al. Minocycline reduces proinflammatory cytokine expression, microglial activation, and caspase-3 activation in a rodent model of diabetic retinopathy. Diabetes. 2005;54(5):1559–65. https://doi.org/10.2337/diabetes.54.5.1559.
46. Wooff Y, Man SM, Aggio-Bruce R, Natoli R, Fernando N. IL-1 family members mediate cell death, inflammation and angiogenesis in retinal degenerative diseases. Front Immunol. 2019. https://doi.org/10.3389/fimmu.2019.01618.
47. Rodríguez-Ramírez KT, Norte-Muñoz M, Lucas-Ruiz F, Gallego-Ortega A, Calzaferri F, García-Bernal D, et al. Retinal response to systemic inflammation differs between sexes and neurons. Front Immunol. 2024. https://doi.org/10.3389/fimmu.2024.1340013.
48. Sorokin V, Vickneson K, Kofidis T, Woo CC, Lin XY, Foo R, et al. Role of vascular smooth muscle cell plasticity and interactions in vessel wall inflammation. Front Immunol. 2020;11: 599415. https://doi.org/10.3389/fimmu.2020.599415.
49. Raines EW. The extracellular matrix can regulate vascular cell migration, prolife ration, and survival: relationships to vascular disease. Int J Exp Pathol. 2000;81(3):173–82. https://doi.org/10.1046/j.1365-2613.2000.00155.x.
50. Giacomini E, Minetto S, Li Piani L, Pagliardini L, Somigliana E, Viganò P. Genetics and inflammation in endometriosis: improving knowledge for development of new pharmacological strategies. Int J Mol Sci. 2021. https://doi.org/10.3390/ijms22169033.
51. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, et al. Inflammatory mechanisms contributing to endothelial dysfunction. Biomedicines. 2021. https://doi.org/10.3390/biomedicines9070781.
52. Luo HR, Loison F. Constitutive neutrophil apoptosis: mechanisms and regulation. Am J Hematol. 2008;83(4):288–95. https://doi.org/10.1002/ajh.21078.
53. Cristiani C, Volpi D, Landonio A, Bertolero F. Endothelin-1-selective binding sites are downregulated by transforming growth factor-beta and upregulated by basic fibroblast growth factor in a vascular smooth muscle-derived cell line. J Cardiovasc Pharmacol. 1994;23(6):988–94. https://doi.org/10.1097/00005344-199406000-00018.
54. Cui S, Men L, Li Y, Zhong Y, Yu S, Li F, et al. Selenoprotein S attenuates tumor necrosis factor-α-induced dysfunction in endothelial cells. Mediators Inflamm. 2018;2018:1625414. https://doi.org/10.1155/2018/1625414.
55. Yolanda M, Donosepoetro M, Santoso A. Relationship of endothelin-1, tumor necrosis factor-alpha and interleukin-6 with the progression of heart failure. Indones Biomed J. 2009;1:45–50. https://doi.org/10.18585/inabj.v1i2.93.
56. Wang X-N, Li T-T, Long D, et al. Peripapillary vessel density and retinal nerve fiber layer thickness c hanges in early diabetes retinopathy. Int J Ophthalmol. 2022;15(9):1488–95. https://doi.org/10.18240/ijo.2022.09.12.
57. Mokrane A, Zureik A, Bonnin S, Erginay A, Lavia C, Gaudric A, et al. Retinal sensitivity correlates with the superficial vessel density and inner layer thickness in diabetic retinopathy. Invest Ophthalmol Vis Sci. 2021;62(14):28. https://doi.org/10.1167/iovs.62.14.28.
58. Jia W, Xu L, Xu W, Yang M, Zhang Y. Application of nanotechnology in the diagnosis and treatment of acute pancreatitis. Nanoscale Adv. 2022;4(8):1949–61. https://doi.org/10.1039/d2na00020b.
59. Khatkov I, Tyulyaeva E, Les'ko K, Dubtsova E, Bordin D, Kiriukova M, et al. Early diagnosis of chronic pancreatitis. Almanac Clin Med. 2022. https://doi.org/10.18786/2072-0505-2022-50-049.

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