tvst

Retina

Choroidal Vascularity Index and Choroidal Structural Changes in Children With Nephrotic Syndrome

Wenbo Zhang[1,*], Junmeng Li[1,*], Lei Zhu[2,3], Shuang Zeng[2,3], Yanye Lu[2,3], Yadi Zhang[1], Xiaopeng Gu[1], Hailong Wu[1], and Liu Yang[1]

[1] Department of Ophthalmology, Peking University First Hospital, Beijing, China
[2] Institute of Medical Technology, Peking University Health Science Center, Peking University, Beijing, China
[3] National Biomedical Imaging Center, Peking University, Beijing, China

Correspondence: Liu Yang, Department of Ophthalmology, Peking University First Hospital, No. 8 Xishiku Street, Xicheng District, Beijing 100034, China. e-mail: liu_yang@bjmu.edu.cn

Received: September 27, 2023
Accepted: February 11, 2024
Published: March 21, 2024

Keywords: nephrotic syndrome; choroidal vascularity index; albumin; transferrin; optical coherence tomography

Citation: Zhang W, Li J, Zhu L, Zeng S, Lu Y, Zhang Y, Gu X, Wu H, Yang L. Choroidal vascularity index and choroidal structural changes in children with nephrotic syndrome. Transl Vis Sci Technol. 2024;13(3):18, https://doi.org/10.1167/tvst.13.3.18

Purpose: To investigate the choroidal vascularity index (CVI) and choroidal structural changes in children with nephrotic syndrome.

Methods: This was a cross-sectional study involving 45 children with primary nephrotic syndrome and 40 normal controls. All participants underwent enhanced depth imaging–optical coherence tomography examinations. An automatic segmentation method based on deep learning was used to segment the choroidal vessels and stroma, and the choroidal volume (CV), vascular volume (VV), and CVI within a 4.5 mm diameter circular area centered around the macular fovea were obtained. Clinical data, including blood lipids, serum proteins, renal function, and renal injury indicators, were collected from the patients.

Results: Compared with normal controls, children with nephrotic syndrome had a significant increase in CV (nephrotic syndrome: 4.132 $\pm$ 0.464 vs. normal controls: 3.873 $\pm$ 0.574; $P = 0.024$); no significant change in VV (nephrotic syndrome: 1.276 $\pm$ 0.173 vs. normal controls: 1.277 $\pm$ 0.165; $P = 0.971$); and a significant decrease in the CVI (nephrotic syndrome: 0.308 [range, 0.270–0.386] vs. normal controls: 0.330 [range, 0.288–0.387]; $P < 0.001$). In the correlation analysis, the CVI was positively correlated with serum total protein, serum albumin, serum prealbumin, ratio of serum albumin to globulin, and 24-hour urine volume and was negatively correlated with total cholesterol, low-density lipoprotein cholesterol, urinary protein concentration, and ratio of urinary transferrin to creatinine (all $P < 0.05$).

Conclusions: The CVI is significantly reduced in children with nephrotic syndrome, and the decrease in the CVI parallels the severity of kidney disease, indicating choroidal involvement in the process of nephrotic syndrome.

Translational Relevance: Our findings contribute to a deeper understanding of how nephrotic syndrome affects the choroid.

Introduction

Primary nephrotic syndrome is a common kidney disease in children, with an overall incidence of approximately 3/100,000. The pathogenesis of the disease is related to the increased permeability of the glomerular basement membrane to albumin, resulting in massive proteinuria, hypoproteinemia, and edema. Common complications include hyperlipidemia, hypercoagulability, and thrombosis, as well as infection.[1]

Nephrotic syndrome can also affect the eyes. Fluid retention associated with hypoproteinemia can affect the fundus, leading to serous macular detachment and macular edema.[2–4] Edema can also occur in the ciliary body, causing ciliary body–choroidal detachment and angle closure.[3] A hypercoagulable state or abnormal blood lipids may induce retinal artery and vein occlusion[5,6] and Purtscher-like retinopathy.[4] Other ocular complications include conjunctival edema,[3] bacterial conjunctivitis, and glucocorticoid-related glaucoma and cataracts.[7]

There are similarities in genetics, structure, and development between the eyes and kidneys, and, similarly, there is a close link between kidney disease and eye disease. Many studies have confirmed that chronic kidney disease is associated with diabetic retinopathy, age-related macular degeneration, cataract, and glaucoma; retinal microvascular parameters measured by noninvasive fundus imaging are also closely related renal indicators of kidney disease.[8] Previous studies have shown that the vascular density of the retinal capillary plexus is reduced in patients with nephrotic syndrome; in addition, the changes in the vascular density of the retinal capillary plexus parallel the severity of renal injury.[9,10] The choroid is one of the richest vascular structures in the human body, and its health is closely related to eye and systemic conditions.[11,12] In addition, the choroid and glomerulus have a wide vascular network with similar structures.[8] However, the changes in choroidal vessels in nephrotic syndrome are still unknown.

With the advent of enhanced depth imaging–optical coherence tomography (EDI-OCT), the fine structures of deep choroidal vessels can be noninvasively and quickly visualized. In recent years, the choroidal vascularity index (CVI) has emerged as a new parameter for quantifying the choroidal vessels, defined as the ratio of vascular area to total choroidal area or the ratio of vascular volume to total choroidal volume. Compared to traditional choroidal markers such as choroidal thickness, the CVI is a more stable and reliable marker for studying the choroid. It can resist the influence of other physiological parameters, such as age, axial length, intraocular pressure, and blood pressure, and it is not affected by the OCT examination modality (spectral domain or swept source).[11,12] By dividing the choroid into vascular and stromal regions, relevant information on choroidal structural changes can also be displayed.

In this study, we investigated the CVI and choroidal structural changes in children with nephrotic syndrome and explored whether these parameters are correlated with clinical indicators of renal function and renal injury to investigate whether nephrotic syndrome affects the choroid.

Materials and Methods

Study Design and Population

This was a cross-sectional, single-center study. Forty-five children with primary nephrotic syndrome diagnosed at Peking University First Hospital between 2017 and 2018 were included in the study. The diagnostic criteria were as follows: urine protein excretion $\geq$ 50 mg/kg/d, random urine sample with 3 to 4+ protein by dipstick examination at least three times a week, ratio of urinary protein to creatinine $\geq$ 2 mg/mg, and serum albumin $<$ 25 g/L.[13] Children who had a first onset of nephrotic syndrome, were undergoing treatment, or who had relapsed were all included. Children with secondary nephrotic syndrome, hematological disorders, endocrine disorders, autoimmune diseases, heritable disease, uncontrollable hypertension, urinary tract infection, obstructive sleep apnea syndrome, and severe organ dysfunction were excluded. Children with poorly controlled glaucoma; severe cataracts; retinal, optic nerve, or choroidal lesions; intraocular inflammation; refractive errors exceeding $\pm$3 D; or a history of surgery or trauma in the eye were also excluded. Forty normal children were selected as healthy controls. This study followed the tenets of the Declaration of Helsinki and was approved by the National Unit of Clinical Trial Ethics Committee, Peking University First Hospital. Informed consent was obtained from all parents or legal guardians of the children prior to the start of the study.

Data Collection

Ophthalmic Data Collection

All children underwent detailed ophthalmic examinations, including best-corrected visual acuity, noncontact intraocular pressure (CT-1P; Topcon, Tokyo, Japan), slit-lamp biomicroscopy and fundoscopic examinations, and axial length measurement (IOLMaster 500; Carl Zeiss Meditec, Jena, Germany). EDI-OCT (Heidelberg Engineering, Heidelberg, Germany) examinations were also performed for all participants. All examinations were conducted by an experienced technician between 2 PM and 4 PM in the afternoon after each participant's pupils had been dilated. EDI-OCT volume raster scans, consisting of 19 horizontal B-scans, were performed through the fovea, with a scanning interval of 240 µm. Volume raster scans covered a visual field of 4.5 $\times$ 6 mm centered around the fovea. To improve the signal-to-noise ratio, automatic real-time tracking was used with 30 frames averaged for each B-scan (automatic real time [ART] = 30). Each B-scan included 768 A-scans. All B-scan images obtained had to be sufficiently clear to allow segmentation of the choroidal vessels and stroma.

A circular area with a diameter of 4.5 mm centered around the macular fovea was selected as the region of interest (ROI), and the choroidal biomarkers of this region were measured (Fig. 1A). By segmenting the choroidal vessels and stroma from multiple

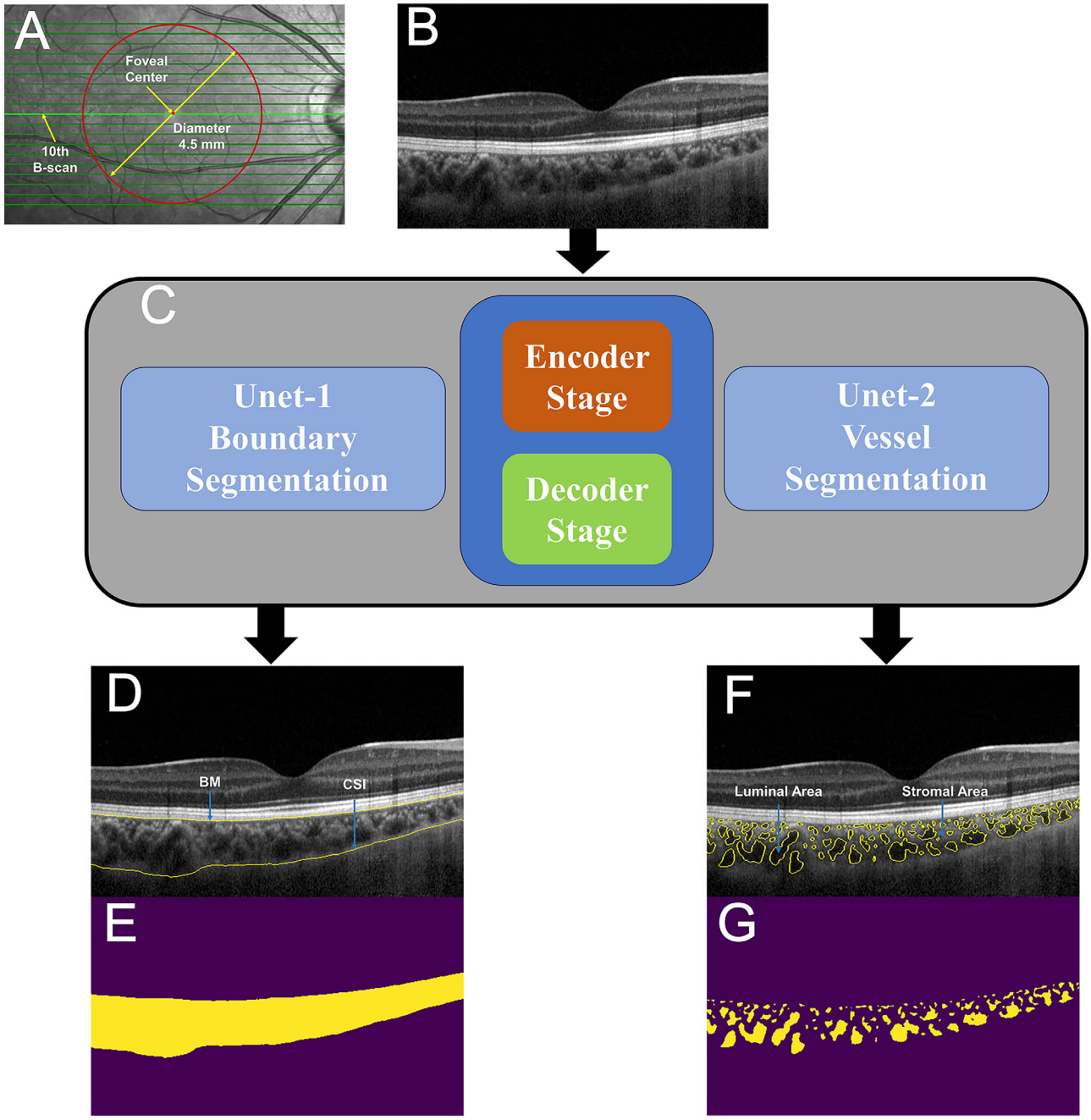

Figure 1. Schematic diagram of the automatic segmentation of choroidal boundaries and blood vessels. (**A**) Near-infrared reflectance image showing the 19 B-scans of EDI-OCT volume raster scans, the foveal center, and the ROI area with a diameter of 4.5 mm centered around the macular fovea. (**B**) Unsegmented original B-scan image. (**C**) Unet structure for choroidal segmentation. (**D**, **E**) Choroidal boundary segmentation and visualization of B-scan image. (**F**, **G**) Choroidal vessel segmentation and visualization of B-scan image. BM, Bruch's membrane; CSI, choroidoscleral interface.

B-scan images, a total of three choroidal biomarkers can be obtained: choroidal volume (CV), vascular volume (VV), and CVI. CV refers to the total volume of the choroid in the ROI area, VV refers to the volume of the choroidal vascular lumen in the ROI area, and the CVI is the ratio of VV to CV. We used an automatic segmentation method based on deep learning to segment the choroidal vessels and stroma instead of manual segmentation.[14,15]

The manually labeled B-scan images are input into two deep convolutional neural networks (DCNNs) to segment the choroidal boundary and vessel; these networks include an encoder stage for extracting high-level features and a decoder stage for reconstructing

the image resolution. After training, the two DCNNs can accurately segment the choroidal boundary and vessels from each B-scan image and calculate the VV, CV, and CVI automatically (Fig. 1). Previous studies have shown that, compared to manual segmentation, this automatic method for segmenting the choroidal boundary and vessels is highly accurate (>0.980). The detailed working principle can be found in previous publications.[14,15]

Clinical Indicator Collection

All laboratory tests were conducted in the central laboratory of Peking University First Hospital. Fasting venous blood was collected from all children. Total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum creatinine, urea, uric acid, serum total protein, serum albumin, serum prealbumin, and the ratio of serum albumin to globulin were measured. All children provided morning and 24-hour urine samples. Urinary protein concentration, urinary creatinine, 24-hour urine volume, and kidney injury indicators (urinary albumin/urinary creatinine, urinary transferrin/urinary creatinine, urinary *N*-acetyl-β-D-glucosaminidase/urinary creatinine, and urinary α-1-microglobulin/urinary creatinine) were obtained. The 24-hour urinary total protein (g/24 h) was calculated by the following formula: 24-hour urine volume (L/24 h) × urinary protein concentration (g/L). The 24-hour creatinine clearance rate (mL/min) was calculated by the following formula: urine volume (mL/min) × urinary creatinine (μmol/L)/serum creatinine (μmol/L).

Statistical Analysis

All data were analyzed using SPSS Statistics 21.0 (IBM, Chicago, IL, USA), and only the data from the left eye of the participants were selected for analysis. The Shapiro–Wilk method was used to detect normality. Continuous variables are expressed as mean ± standard deviation for variables with a normal distribution or as median (range of minimum to maximum) for variables with a nonnormal distribution, where appropriate, and categorical variables are presented as numbers. Differences in population characteristics, ocular biological parameters, and choroidal biomarkers between the nephrotic syndrome group and the normal control group were compared using independent samples *t*-tests, Mann–Whitney *U* tests, or χ^2 tests accordingly. The correlation between choroidal biomarkers and clinical indicators in patients with nephrotic syndrome was assessed using Spearman's correlation tests. $P < 0.05$ was considered to indicate statistical significance.

Results

In total, 45 children with nephrotic syndrome (32 males and 13 females; median age, 8 [3–15] years; median course of disease, 2.25 years [6 days–11 years]) and 40 normal controls (25 males and 15 females; median age, 9 [5–16] years) were included in the study. In patients with nephrotic syndrome, the median serum albumin was 20.90 (12.50–41.60) g/L, the median serum creatinine was 44.1 (24.10–152.2) μmol/L, and the median 24-hour urinary total protein was 2.45 (0.02–13.05) g/24 h. The clinical indicators of the children with nephrotic syndrome are shown in Table 1.

Demographic characteristics and ocular biological parameters of the children with nephrotic syndrome and normal controls are shown in Table 2. There were no significant differences in age, sex, best-corrected visual acuity, intraocular pressure, or axial length between children with nephrotic syndrome and normal controls.

A comparison of choroidal biomarkers between the two groups of participants is shown in Table 3. There was no significant difference in VV between the nephrotic syndrome group and the normal control group. The CV of children with nephrotic syndrome was significantly higher than that of normal controls. The CVI of children with nephrotic syndrome was significantly lower than that of normal controls (nephrotic syndrome: 0.308 [0.270–0.386]; normal controls: 0.330 [0.288–0.387]; $P < 0.001$) (Fig. 2).

The results of the correlation analysis between clinical indicators and CVI in children with nephrotic syndrome are shown in Figure 3. The CVI was positively correlated with serum total protein, serum albumin, serum prealbumin, ratio of serum albumin to globulin, and 24-hour urine volume and was negatively correlated with total cholesterol, low-density lipoprotein cholesterol, urinary protein concentration, and ratio of urinary transferrin to creatinine (all $P < 0.05$). None of the other clinical indicators was correlated with the CVI. There was no correlation between VV and CV and any clinical indicators in this study.

Discussion

In this study, we investigated the CVI and choroidal structural changes in children with nephrotic syndrome. The CVIs used in previous studies were usually two-dimensional values obtained through a binarization algorithm on a single B-scan passing through the macular fovea. The measured area (ROI) was often the choroid with a width of 1.5 mm below the

Table 1. Clinical Indicators of Children With Nephrotic Syndrome

Clinical Indicator	Value
Total cholesterol (mmol/L), mean ± SD	9.78 ± 2.81
Triglyceride (mmol/L), mean ± SD	2.71 ± 1.47
Low-density lipoprotein cholesterol (mmol/L), mean ± SD	5.83 ± 2.20
High-density lipoprotein cholesterol (mmol/L), mean ± SD	2.07 ± 0.63
Serum total protein (g/L), mean ± SD	51.68 ± 10.07
Serum albumin (g/L), median (range)	20.90 (12.50–41.60)
Serum prealbumin (g/L), mean ± SD	251.97 ± 130.39
Serum albumin to globulin ratio, median (range)	0.75 (0.48–1.36)
Serum creatinine (μmol/L), median (range)	44.1 (24.10–152.2)
Urea (mmol/L), median (range)	5.29 (2.34–23.80)
Uric acid (μmol/L), median (range)	362.42 (217.00–654.00)
Urinary protein concentration (g/L), median (range)	1.77 (0.01–11.92)
Urinary creatinine (mmol/L), median (range)	5 (1.8–22.9)
24-Hour urine volume (mL/24 h), mean ± SD	1309.38 ± 579.66
24-Hour urinary total protein (g/24 h), median (range)	2.45 (0.02–13.05)
24-Hour creatinine clearance rate (mL/min), median (range)	68.61 (33.81–153.00)
Ratio of urinary albumin to creatinine (mg/g), mean ± SD	3922.31 ± 2798.84
Ratio of urinary transferrin to creatinine (mg/g), mean ± SD	343.42 ± 237.13
Ratio of urinary *N*-acetyl-β-D-glucosaminidase to creatinine (U/g), mean ± SD	73.57 ± 46.78
Ratio of urinary α-1-microglobulin to creatinine (mg/g), median (range)	25.50 (2.57–199.95)

Table 2. Demographic Characteristics and Ocular Biological Parameters of the Participants

	Nephrotic Syndrome	Normal Control	*P*
Age (y), median (range)	8 (3–15)	9 (5–16)	0.521[a]
Sex (male/female), *n*	32/13	25/15	0.399[b]
BCVA (Snellen test), median (range)	1.0 (0.4–1.2)	1.0 (0.8–1.2)	0.125[a]
Intraocular pressure (mmHg), median (range)	18.0 (14.0–30.0)	17.0 (12.0–21.0)	0.078[a]
Axial length (mm), median (range)	23.1 (20.4–24.7)	23.2 (21.7–24.5)	0.669[a]

BCVA, best-corrected visual acuity.
[a]Mann–Whitney *U* test.
[b]χ^2 test.

Table 3. Choroidal Biomarkers of the Participants

	Nephrotic Syndrome	Normal Control	*P*
VV, mean ± SD	1.276 ± 0.173	1.277 ± 0.165	0.971[a]
CV, mean ± SD	4.132 ± 0.464	3.873 ± 0.574	0.024[a]
CVI, median (range)	0.308 (0.270–0.386)	0.330 (0.288–0.387)	<0.001[b]

[a]Independent samples *t*-test.
[b]Mann–Whitney *U* test.

macular fovea.[12] Our study obtained three-dimensional CVIs through volume scanning covering a circular area with a diameter of 4.5 mm. These results contain more volumetric information on the choroid and provide a more comprehensive reflection of the condition of the choroidal vasculature.[16–18]

Many studies have shown that the CVI is a promising metric for early diagnosis, disease prediction, and disease progress monitoring, and it is widely used when investigating various eye diseases, such as age-related macular degeneration, central serous chorioretinopathy, diabetic retinopathy, uveitis, retinitis

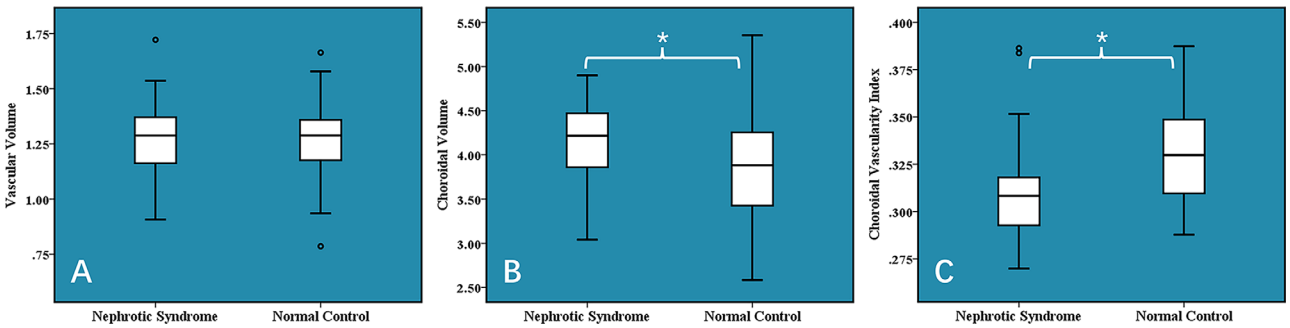

Figure 2. Comparison of choroidal biomarkers between children with nephrotic syndrome and normal controls: (**A**) vascular volume, (**B**) choroidal volume, and (**C**) choroidal vascularity index. The asterisk (*) represents a significant difference between the two groups.

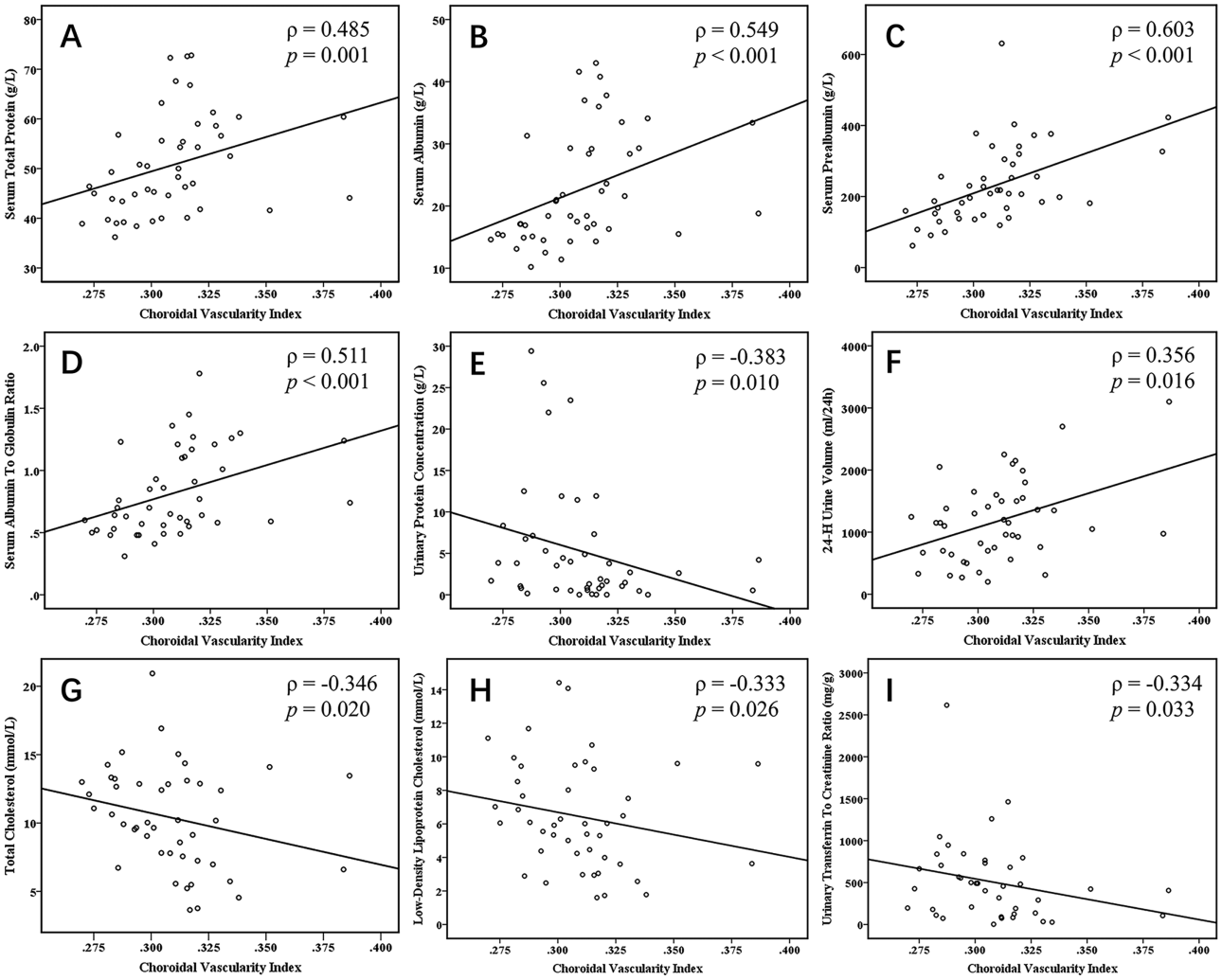

Figure 3. Correlations between clinical indicators and the choroidal vascularity index of patients with nephrotic syndrome: (**A**) serum total protein, (**B**) serum albumin, (**C**) serum prealbumin, (**D**) ratio of serum albumin to globulin, (**E**) urinary protein concentration, (**F**) 24-hour urine volume, (**G**) total cholesterol, (**H**) low-density lipoprotein cholesterol, and (I) ratio of urinary transferrin to creatinine.

pigmentosa, glaucoma, ischemic optic neuropathy, and pathological myopia.[11,12] In addition, many studies have shown that the CVI is also altered in individuals with several systemic diseases, such as Alport syndrome,[19] allergic asthma,[20] obsessive–compulsive disorder,[21] hypertension,[22] multiple sclerosis,[23] Parkinson's disease,[24] obstructive sleep apnea syndrome,[25] coronary artery disease,[26] and internal carotid artery stenosis.[27] Compared to traditional choroidal markers such as choroidal thickness, the CVI is more stable

and reliable. Segmentation of the choroidal vessels and stroma can also reflect the states and relationships of the choroidal blood vessels and stroma. Therefore, the CVI provides additional information for studying the impact of systemic diseases on the choroid.

In this study, we found that the CVI was decreased in children with nephrotic syndrome relative to the control children. Although there is a definite correlation between kidney disease and fundus disease, research on the relationship between CVI and kidney disease is rare, and the outcome is inconclusive. Han et al.[28] suggested that a reduction in the CVI is an independent risk factor for diabetic nephropathy. Their research found that, among patients with diabetes, the CVI of patients with diabetic nephropathy was significantly lower than that of patients without diabetic nephropathy. As the pathological staging of kidney disease gradually deteriorates, the CVI decreases accordingly. Compared with diabetic retinopathy, the CVI is a more reliable means to predict the pathological stages of diabetic nephropathy. However, some studies do not support the correlation between the CVI and kidney disease. For example, a number of studies have shown that there is no significant difference in the CVI between nephrotic patients who require kidney transplantation due to Alport syndrome and patients who do not require kidney transplantation.[19] Other studies have shown that the CVI is not correlated with renal function indicators such as creatinine, urinary albumin, and estimated glomerular filtration rate.[29] These discrepancies may be attributed to differences in the populations included in the study, the inclusion criteria, the CVI measurement methods, the type of kidney disease, and so on.

It is not entirely clear how nephrotic syndrome affects the CVI. The main pathogenesis of nephrotic syndrome is the loss of plasma albumin from the glomerulus, leading to hypoproteinemia and tissue edema. In the correlation analysis, we found a significant positive correlation between the CVI and plasma total protein, albumin, prealbumin, and the albumin to globulin ratio. Therefore, we speculate that the changes in the CVI are related to the decrease in the plasma albumin. There are pores in the walls of the choroidal blood vessels that allow passage of macromolecular proteins; therefore, the choroidal stroma is rich in protein and has a high colloidal osmotic pressure.[30] When patients with nephrotic syndrome experience hypoalbuminemia, the albumin in the blood vessels decreases, as does the colloid osmotic pressure in the blood vessels. The osmotic pressure difference between the choroidal vessels and the stroma can cause the fluid in the choroidal vessels to flow to the choroidal stroma, causing choroidal edema and thickening. Our study showed that the CV of patients with nephrotic syndrome was significantly higher than that of the normal control group, which also confirmed this hypothesis. Unlike CV, VV did not differ significantly between the nephrotic syndrome group and the control group. This finding suggests that, even if the fluid moves from the choroidal vessels to the stroma due to the increased colloid osmotic gradient, the choroidal blood volume remains unchanged. Most studies have shown that the majority of edematous patients with nephrotic syndrome have a normal intravascular volume, with only a few patients experiencing blood volume depletion.[31] A healthy choroidal vascular system is crucial for ensuring the normal function of the retinal pigment epithelium and outer retina. Some scholars believe that choroidal vessels have autoregulatory ability and can stabilize choroidal perfusion in response to environmental changes.[25,32,33] These findings may explain why there was no significant change in VV in patients with nephrotic syndrome, but the specific mechanism still requires further research. CV increases while VV does not significantly change, resulting in a decrease in the CVI.

In addition to plasma proteins, we also found that the CVI of patients with nephrotic syndrome was positively correlated with 24-hour urine volume and negatively correlated with total cholesterol, low-density lipoprotein cholesterol, urinary protein concentration, and ratio of urinary transferrin to creatinine. Transferrin (molecular weight, 76,500 kDa) is a protein with a weight similar to albumin. Due to its higher isoelectric point than albumin, it is less repelled by polyanion in the glomerulus and more easily filters into the renal capsule. Therefore, it is excreted earlier or at a higher proportion than albumin. Currently, it is believed that urinary transferrin is a more sensitive marker of glomerular injury than urinary albumin.[34,35] Some studies have also shown that the excretion of urinary transferrin in patients with diabetic retinopathy is significantly higher than that in patients without retinopathy,[36] indicating that this marker may also have some association with retinopathy. Patients with nephrotic syndrome often have oliguria and hyperlipidemia. The decrease in urine volume and the increase in blood lipids also reflect the severity of nephrotic syndrome. Therefore, the results of this study indicate that the changes in the CVI parallel the severity of nephrotic syndrome and the degree of glomerular injury. One study showed that choroidal thickness is related to renal function and renal injury.[37] Our research further confirmed the close relationship between renal dysfunction and changes in choroidal microcirculation. And the CVI helps us understand how nephrotic syndrome affects

the choroid. Retinal microvascular abnormalities are often used as markers for predicting renal function decline.[38,39] In the future, further research can be conducted to determine whether alterations in the CVI can predict the outcome of nephrotic syndrome and whether alterations in the CVI are related to different pathological types of nephrotic syndrome. If the results are meaningful, the CVI could serve as a biomarker for nephrotic syndrome.

This study has several limitations. First, this study was limited by its single-center nature, and the sample size was also small. Second, due to the cross-sectional design of this study, the causal relationship between CVI and nephrotic syndrome cannot yet be determined. Third, the results of this study reflect only the characteristics of the CVI in children with nephrotic syndrome. Whether similar results can be extrapolated to other types of kidney diseases, such as glomerulonephritis and diabetic nephropathy, remains unknown and requires further exploration. Finally, the specific biological mechanisms underlying the correlation between CVI and nephrotic syndrome have not yet been elucidated, and additional experiments are needed.

In conclusion, the CVI is significantly reduced in children with nephrotic syndrome, and the decrease in the CVI parallels the severity of kidney disease, indicating that the choroid is involved in the process of nephrotic syndrome. Our study confirmed the close relationship between choroidal microcirculation changes and renal dysfunction in nephrotic syndrome.

Acknowledgments

Supported by a grant from the National Natural Science Foundation of China (82171059).

Disclosure: **W. Zhang**, None; **J. Li**, None; **L. Zhu**, None; **S. Zeng**, None; **Y. Lu**, None; **Y. Zhang**, None; **X. Gu**, None; **H. Wu**, None; **L. Yang**, None

* WZ and JL contributed equally to this work.

References

1. Mattoo TK, Sanjad S. Current understanding of nephrotic syndrome in children. *Pediatr Clin North Am*. 2022;69(6):1079–1098.
2. Tsani Z, Ntafos A, Toumanidou V, Dastiridou A, Ploumi I, Androudi S. Vision loss in a pregnant woman with nephrotic syndrome [published online ahead of print October 19, 2021]. *Eur J Ophthalmol*, https://doi.org/10.1177/11206721211054731.
3. Takai Y, Sakuma T, Mashimo K, Inoue K, Ebihara N. A case of nephrotic syndrome with bilateral serous retinal detachment and shallow anterior chamber associated with ciliary body edema. *Case Rep Ophthalmol*. 2022;13(3):949–955.
4. Govindaraju VK, Trese MGJ, Faia LJ. Ocular complications of acute worsening of nephrotic syndrome. *Ophthalmic Surg Lasers Imaging Retina*. 2022;53(7):393–396.
5. Padhy SK, Padhi TR, Bhusal U, Panda KG. Bilateral branch retinal artery occlusion in a child with nephrotic syndrome. *BMJ Case Rep*. 2020;13(5):e235689.
6. Sinha S, Rau ATK, Kumar RV, Jayadev C, Vinekar A. Bilateral combined central retinal artery and vein occlusion in a 3-year-old child with nephrotic syndrome. *Indian J Ophthalmol*. 2018;66(10):1498–1501.
7. Nakubulwa F, Lusobya RC, Batte A, et al. Prevalence and predictors of ocular complications among children undergoing nephrotic syndrome treatment in a resource-limited setting. *BMC Ophthalmol*. 2021;21(1):55.
8. Wong CW, Wong TY, Cheng CY, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. *Kidney Int*. 2014;85(6):1290–1302.
9. Yao T, He Y, Huang L, et al. Quantitative vessel density analysis of macular and peripapillary areas by optical coherence tomography angiography in adults with primary nephrotic syndrome. *Microvasc Res*. 2022;144:104407.
10. Zhang W, Kang L, Zhang Y, et al. Quantitative analysis of retinal and choroidal microvascular parameters using optical coherence tomography angiography in children with nephrotic syndrome: a pilot study. *Graefes Arch Clin Exp Ophthalmol*. 2020;258(2):289–296.
11. Agrawal R, Ding J, Sen P, et al. Exploring choroidal angioarchitecture in health and disease using choroidal vascularity index. *Prog Retin Eye Res*. 2020;77:100829.
12. Betzler BK, Ding J, Wei X, et al. Choroidal vascularity index: a step towards software as a medical device. *Br J Ophthalmol*. 2022;106(2):149–155.
13. Nephrology Group, Chinese Paediatric Society, Chinese Medical Association. Evidence-based guideline for the diagnosis and treatment of steroid-sensitive, relapse/dependent nephrotic syndrome in children (2016). *Chin J Pediatr*. 2017;10(55):729–734.

14. Li J, Zhu L, Zhu R, et al. Automated analysis of choroidal sublayer morphologic features in myopic children using EDI-OCT by deep learning. *Transl Vis Sci Technol*. 2021;10(13):12.
15. Zhu L, Li J, Zhu R, et al. Synergistically segmenting choroidal layer and vessel using deep learning for choroid structure analysis. *Phys Med Biol.* 2022;67(8):085001.
16. Liu L, Zhu C, Yuan Y, et al. Three-dimensional choroidal vascularity index in high myopia using swept-source optical coherence tomography. *Curr Eye Res*. 2022;47(3):484–492.
17. Chen L, Yuan M, Sun L, Chen Y. Three-dimensional analysis of choroidal vessels in the eyes of patients with unilateral BRVO. *Front Med (Lausanne)*. 2022;9:854184.
18. Zeng Q, Luo L, Yao Y, Tu S, Yang Z, Zhao M. Three-dimensional choroidal vascularity index in central serous chorioretinopathy using ultra-widefield swept-source optical coherence tomography angiography. *Front Med (Lausanne)*. 2022;9:967369.
19. Cicinelli MV, Ritter M, Tausif H, et al. Characterization of choriocapillaris and choroidal abnormalities in alport syndrome. *Transl Vis Sci Technol*. 2022;11(3):23.
20. Yilmaz M, Polat OA, Karayigit DZ, Ayyildiz T. Choroidal vascularity index and choroidal thickness changes in patients with allergic asthma. *Photodiagnosis Photodyn Ther*. 2021;36: 102494.
21. Sekeryapan Gediz B, Ozturk M, Kilinc Hekimsoy H, Yuksel EG, Ozdamar Erol Y. Choroidal vascularity index as a potential inflammatory biomarker for obsessive compulsive disorder. *Ocul Immunol Inflamm*. 2022;30(2):428–432.
22. Asikgarip N, Temel E, Kivrak A, Ornek K. Choroidal structural changes and choroidal vascularity index in patients with systemic hypertension. *Eur J Ophthalmol*. 2022;32(4):2427–2432.
23. Balci S, Ozcelik Kose A, Yenerel NM. The effect of optic neuritis attacks on choroidal vascularity index in patients with multiple sclerosis. *Graefes Arch Clin Exp Ophthalmol*. 2021;259(8):2413–2424.
24. Robbins CB, Thompson AC, Bhullar PK, et al. Characterization of retinal microvascular and choroidal structural changes in Parkinson disease. *JAMA Ophthalmol*. 2021;139(2):182–188.
25. Altinel MG, Uslu H, Kanra AY, Dalkilic O. Effect of obstructive sleep apnoea syndrome and continuous positive airway pressure treatment on choroidal structure. *Eye (Lond)*. 2022;36(10):1977–1981.
26. Seo WW, Yoo HS, Kim YD, Park SP, Kim YK. Choroidal vascularity index of patients with coronary artery disease. *Sci Rep*. 2022;12(1): 3036.
27. Li S, Lang X, Wang W, et al. Choroidal vascular changes in internal carotid artery stenosis: a retrospective cohort study in Chinese population. *BMC Ophthalmol*. 2019;19(1):215.
28. Han X, Du NN, Li S, Diao ZL, Fu L, Liu WH. Choroidal vascularity index assessment: a potential noninvasive technique for diagnosing diabetic nephropathy. *J Ophthalmol*. 2022;2022: 3124746.
29. Kim JT, Lee IG. Correlation of renal profiles with choroidal vascularity index in eyes with diabetic retinopathy. *J Clin Med*. 2021;10(21):5155.
30. Li X. The basis of retinal vascular disease. In: Li X, ed. *Retinal Vascular Disease*. Beijing: People's Medical Publishing House; 2017:50.
31. Siddall EC, Radhakrishnan J. The pathophysiology of edema formation in the nephrotic syndrome. *Kidney Int*. 2012;82(6):635–642.
32. Sevik MO, Çam F, Aykut A, Dericioğlu V, Şahin Ö. Choroidal vascularity index changes during the Valsalva manoeuvre in healthy volunteers. *Ophthalmic Physiol Opt*. 2022;42(2):367–375.
33. Kiel JW, van Heuven WA. Ocular perfusion pressure and choroidal blood flow in the rabbit. *Invest Ophthalmol Vis Sci*. 1995;36(3):579–585.
34. Hong CY, Chia KS. Markers of diabetic nephropathy. *J Diabetes Complications*. 1998;12(1):43–60.
35. Vaziri ND. Erythropoietin and transferrin metabolism in nephrotic syndrome. *Am J Kidney Dis*. 2001;38(1):1–8.
36. Martin P, Tindall H, Harvey JN, Handley TM, Chapman C, Davies JA. Glomerular and tubular proteinuria in type 1 (insulin-dependent) diabetic patients with and without retinopathy. *Ann Clin Biochem*. 1992;29(pt 3):265–270.
37. Mulè G, Vadalà M, La Blasca T, et al. Association between early-stage chronic kidney disease and reduced choroidal thickness in essential hypertensive patients. *Hypertens Res.* 2019;42(7):990–1000.
38. Edwards MS, Wilson DB, Craven TE, et al. Associations between retinal microvascular abnormalities and declining renal function in the elderly population: the Cardiovascular Health Study. *Am J Kidney Dis*. 2005;46(2):214–224.
39. Wong TY, Coresh J, Klein R, et al. Retinal microvascular abnormalities and renal dysfunction: the atherosclerosis risk in communities study. *J Am Soc Nephrol*. 2004;15(9):2469–2476.