Original Article

Corneal endothelial cell density and microvascular changes of retina and optic disc in autosomal dominant polycystic kidney disease

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Purpose: Vascular endothelial dysfunction in autosomal dominant polycystic kidney disease (ADPKD) may affect the retinal vascular parameters due to structural similarities of kidney and retina. We aimed to evaluate the microvascular changes of retina and optic disc and also corneal endothelial cell density in patients with ADPKD. **Methods:** Forty-six eyes of 23 patients with ADPKD (Group 1), and 46 eyes of 23 sex- and age-matched healthy controls (Group 2) were included in this cross-sectional study. Demographic and ophthalmic findings of participants were collected. Corneal endothelial cell density (CECD) measurements were obtained by noncontact specular microscopy. Foveal retinal thickness, peripapillary retinal nerve fiber layer (RNFL) thickness, vessel density in different sections of the retina and optic nerve head were analyzed by optical coherence tomography angiography. **Results:** The mean ages were 41 ± 11 years for Group 1 and 39 ± 10 years for Group 2 (P = 0.313). CECD values were significantly lower in group 1 when compared to group 2 (2653 ± 306 cells/mm^2 and 2864 ± 244 cells/mm^2, respectively, P < 0.001). The foveal retinal thickness and RNFL thickness were similar, but superior quadrant thickness of RNFL was significantly lower in Group 1 than Group 2 (126 ± 14 µm vs. 135 ± 15 µm, P = 0.003). In Group 1, whole image of optic disc radial peripapillary capillary densities were significantly lower compared to Group 2 (49.4 ± 2.04%, and 50.0 ± 2.2%, respectively, P = 0.043). There was no significant difference regarding superficial, deep retinal vessel densities, foveal avascular zone and flow areas between the groups (P > 0.05 for all). **Conclusion:** Lower CECD values and decreased superior quadrant RNFL thickness, and microvascular densities of optic disc were revealed in patients with ADPKD. Evaluation of CECD and retinal microvasculature may be helpful in the management of these patients.

Key words: Cornea endothelial cell density, optic disc, optical coherence tomography angiography, polycystic kidney disease, retina, specular microscopy

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Autosomal dominant polycystic kidney disease (ADPKD), with a prevalence of 1: 400–1000, the most common and the only adult-onset hereditary cystic renal disease.[1-4] The disease results from the mutations of polycystin genes on chromosomes 16 (85%) and 4 (15%).[4] The ADPKD is also a systemic disorder that involves multiple organs including kidney, liver, pancreas, seminal vesicles, meninges, heart, eye, and cerebral anomalies.[4-7]

Specular microscopy is used for corneal endothelium parameters.[7-10] A variety of studies have investigated the morphological and physiological alterations in the corneal endothelium of patients with chronic kidney disease, end-stage renal disease, and receiving hemodialysis.[9,11-16] Although alterations in biomechanical properties such as higher corneal hysteresis in patients with ADPKD have been reported,[1] to date, there is no study evaluating the corneal endothelial specular microscopy findings in these patient population.

Vascular endothelial dysfunction has also been shown in patients with ADPKD.[17] The glomerular filtration barrier and inner blood–retinal barrier have extensive structural similarities.[18] Systemic vascular changes can presumably affect both kidney and the chorioretinal parameters.[19] Optical coherence tomography angiography (OCTA) is a novel innovation that demonstrates microvascular structure of the retina in a non-invasive, rapid, and high-resolution method. To our knowledge, there is no study evaluating the microvascular parameters by using OCTA in ADPKD patients.

The goal of this study was to assess corneal endothelial specular microscopy alterations in ADPKD patients. Given the role of vascular endothelial dysfunction in ADPKD patients, the retinal and optic disc microvascular findings in these patients by OCTA were aimed to investigate and compare with the results of the healthy age- and sex-matched individuals.

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Methods

This cross-sectional study consisted of 46 eyes of 23 patients with ADPKD referred from nephrology outpatient clinic (Group 1), and 46 eyes of 23 sex- and age-matched healthy controls recruited from ophthalmology outpatient clinic (Group 2). Demographic and clinical characteristics, specular microscopy, and the OCTA findings were collected. Signed written informed consent forms were taken from all participants and then complete ophthalmic examinations including measurement of best-corrected visual acuity, refractive error, and as well as slit-lamp biomicroscopy, non-contact tonometry, and fundoscopy were performed. All subjects were examined at the same period of the day (between 10:00-12:00 AM). Patients with a refractive error of ≥±2.00 diopters, history of ocular disease and treatment, trauma or surgery, abnormal axial length as short or long (<21 mm or >27 mm), corneal opacity or dystrophy, glaucoma, pseudoexfoliation, uveitis, use of contact lens, use of topical eye drops, pregnancy, lactation, undergoing hemodialysis, diabetes mellitus, poor-quality OCTA images (image signal strength less than 8 according to the OCTA manufacturer) due to eye movements or media opacities and uncontrolled blood pressure were excluded from the study.

The corneal endothelial cell density, minimum and maximum cell size, average cell size, standard deviation of cell size, coefficient of variation of cell size, and percentage of hexagonality of cells were analyzed for each subject with non-contact specular microscopy (SP-3000 P, Topcon Corporation, Japan) by a single experienced examiner. To evaluate the corneal endothelium, an average of three images of the central cornea per eye per patient was used. Subjects were asked to look at the central fixation target, and at least 100 cells per measurement automatically were included in each analysis.

The OCTA images were obtained by a single technician using a spectral-domain OCT system with the AngioVue OCTA software (Avanti RTVue-XR 100, Optovue Inc, Fremont, CA). This device uses an increased A scan rate of 70 kHz, which allows the generation of high axial resolution of 5 µm in tissue. The OCTA provides vascular information of retinal layers as enface angiogram, a vessel density map and a vessel density percentage (%) calculated as the area covered by flowing blood vessels in the selected region. The OCTA image protocol involved two raster scans covering a 6 × 6 mm area centered on macula and 4.5 × 4.5 mm area centered in optic nerve head. Foveal retinal thickness, retinal nerve fiber layer thickness, vessel density in fovea of superficial and deep capillary plexus, 300 µm width around the foveal avascular zone and radial peripapillary capillary plexus were measured. The area of foveal avascular zone was defined as without vessels that covers the center of the fovea, and automatically calculated by clicking on the center of the foveal avascular zone. Fovea, parafovea, and perifovea were defined as an annulus centered on the foveal avascular zone with inner and outer ring diameters of 1 mm, 1 to 3 mm and 3 to 6 mm, respectively. Flow areas of choriocapillaris were noted, too. Optic disc for radial peripapillary capillary densities including; whole image, inside disc and peripapillar capillary plexus densities, were also obtained. The peripapillary region was defined as a 700-µm wide elliptical annulus extending outward from the optic disc boundary.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 (SPSS, Inc., Chicago, Illinois, USA). Continuous data were expressed as mean ± standard deviation. The Kolmogorov–Smirnov test was used to test the normality of distribution of continuous variables. Continuous variables were compared with the Student's t-test. Categorical data were expressed as number and percentages. To compare categorical data, the Chi-square test was used. A $P < 0.05$ was accepted as statistically important.

Results

Baseline demographic characteristics and clinical data of the study population are summarized in Table 1. The mean ages were 41 ± 11 years for Group 1 and 39 ± 10 years for Group 2 ($P = 0.313$). Gender rates, intraocular pressures, and central corneal thickness levels were similar between the groups. The corneal endothelial cell density values were significantly lower in Group 1 when compared to Group 2 (2653 ± 306 cells/mm^2 and 2864 ± 244 cells/mm^2, respectively, $P < 0.001$). The hexagonality of cells was found to be decreased in Group 1, but the difference was not significant [Table 2]. A specular microscopy image of an age- and sex- matched subject in each group are shown in Fig. 1. There was also no significant difference regarding foveal retinal thickness and retinal nerve fiber layer thickness ($P = 0.4$, and $P = 0.271$, respectively).

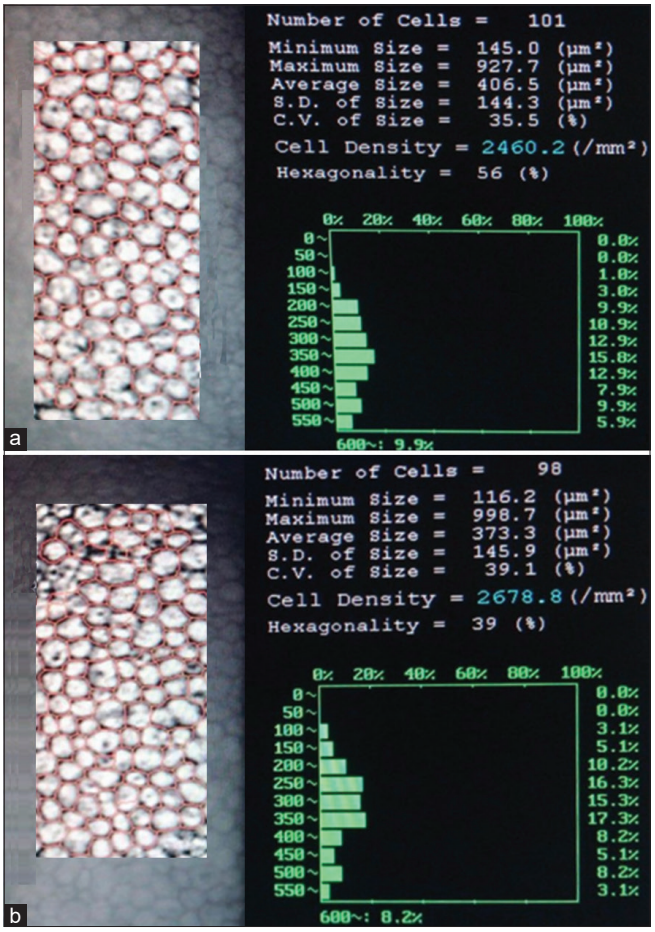

Figure 1: (a) Specular microscopy image of a 42- year-old female patient with autosomal dominant polycystic kidney disease. (b) Specular microscopy image of a 42 years old female healthy control subject

However, superior quadrant thickness of retinal nerve fiber layer was significantly lower in Group 1 than Group 2 (126 ± 14 μm, and 135 ± 15 μm, respectively, P = 0.003). There was no significant difference regarding superficial, deep retinal vessel densities and flow areas between the groups [Table 3]. As shown in Table 4, whole image, inside disc and peripapillary of radial

Table 1: Comparison of demographic and clinical characteristics between the groups

Characteristics	ADPKD Group (Group 1)	Control Group (Group 2)	*P*
Number of subjects, *n*	23	23	
Number of eyes, *n*	46	46	
Age, years (Mean±SD)	41±11	39±10	0.313
Gender, *n* (%)			
Female	10 (43.5)	13 (56.5)	0.376
Male	13 (56.5)	10 (43.5)	
Body mass index (kg/m^2) (Mean±SD)	26.2±4.67	25.8±3.85	0.662
IOP (mmHg) (Mean±SD)	16.1±2.5	16.1±2.1	0.947
CCT (μm) (Mean±SD)	538±25	545±27	0.231
FRT (μm) (Mean±SD)	244±16	247±19	0.400
RNFL thickness (μm) (Mean±SD)	109±12	111±10	0.271
Inferior quadrant (μm) (Mean±SD)	136±19	139±15	0.322
Superior quadrant (μm) (Mean±SD)	126±14	135±15	0.003
Temporal quadrant (μm) (Mean±SD)	76±16	74±10	0.365
Nasal quadrant (μm) (Mean±SD)	98±18	101±16	0.540

SD: Standard deviation, IOP: Intraocular pressure, CCT: Central corneal thickness, FRT: Foveal retinal thickness, RNFL: Retinal nerve fiber layer

Table 2: Comparison of specular microscopy findings between the groups

Characteristics	ADPKD group (Group 1) (*n*=46 eyes)	Control group (Group 2) (*n*=46 eyes)	*P*
Number of cells	106±11	108±12	0.349
Minimum cell area (μm^2)	125±38	111±35	0.07
Maximum cell area (μm^2)	802±166	787±172	0.685
Average cell area (μm^2)	376±59	356±49	0.097
CECD (cells/mm^2)	2653±306	2864.53±244	<0.001
SD (μm^2)	130±26	124±21	0.260
CV (%)	35±6	35±5	0.896
Hex (%)	53.5±7.5	55.3±10.2	0.345

CECD: Corneal endothelial cell density; SD: Standard deviation of cell size; CV: Coefficient of variation in cell size; Hex: Hexagonality of cells

Table 3: Comparison of retinal microvascular parameters between the groups by OCTA

Characteristics	ADPKD group (Group 1) (*n*=46 eyes)	Control group (Group 2) (*n*=46 eyes)	*P*
Superficial Vessel Density (%)	51.5±2.8	51.9±3.4	0.554
Deep Vessel Density (%)	55.9±5.6	54.2±6.3	0.159
FAZ area (mm^2)	0.28±0.0	0.28±0.1	0.628
Flow area for outer retina (mm^2)	0.44±0.24	0.55±0.2	0.056
Flow area for choriocapillaris (mm^2)	2.14±0.0	2.15±0.1	0.635

OCTA: Optical coherence tomography angiography, SD: Standard deviation, FAZ: Area of 300 μm width around the foveal avascular zone

Table 4: Comparison of optic disc microvascular parameters between the groups by OCTA

Characteristics	ADPKD group (Group 1) (*n*=46 eyes)	Control group (Group 2) (*n*=46 eyes)	*P*
RPC density (%)			
Whole image	49.4±2.0	50.3±2.2	0.043
Inside disc	49.6±4.2	50.6±3.9	0.279
Peripapillary	51.7±2.4	52.2±2.5	0.278

OCTA: Optical coherence tomography angiography, SD: Standard deviation, RPC: Radial peripapillary capillary

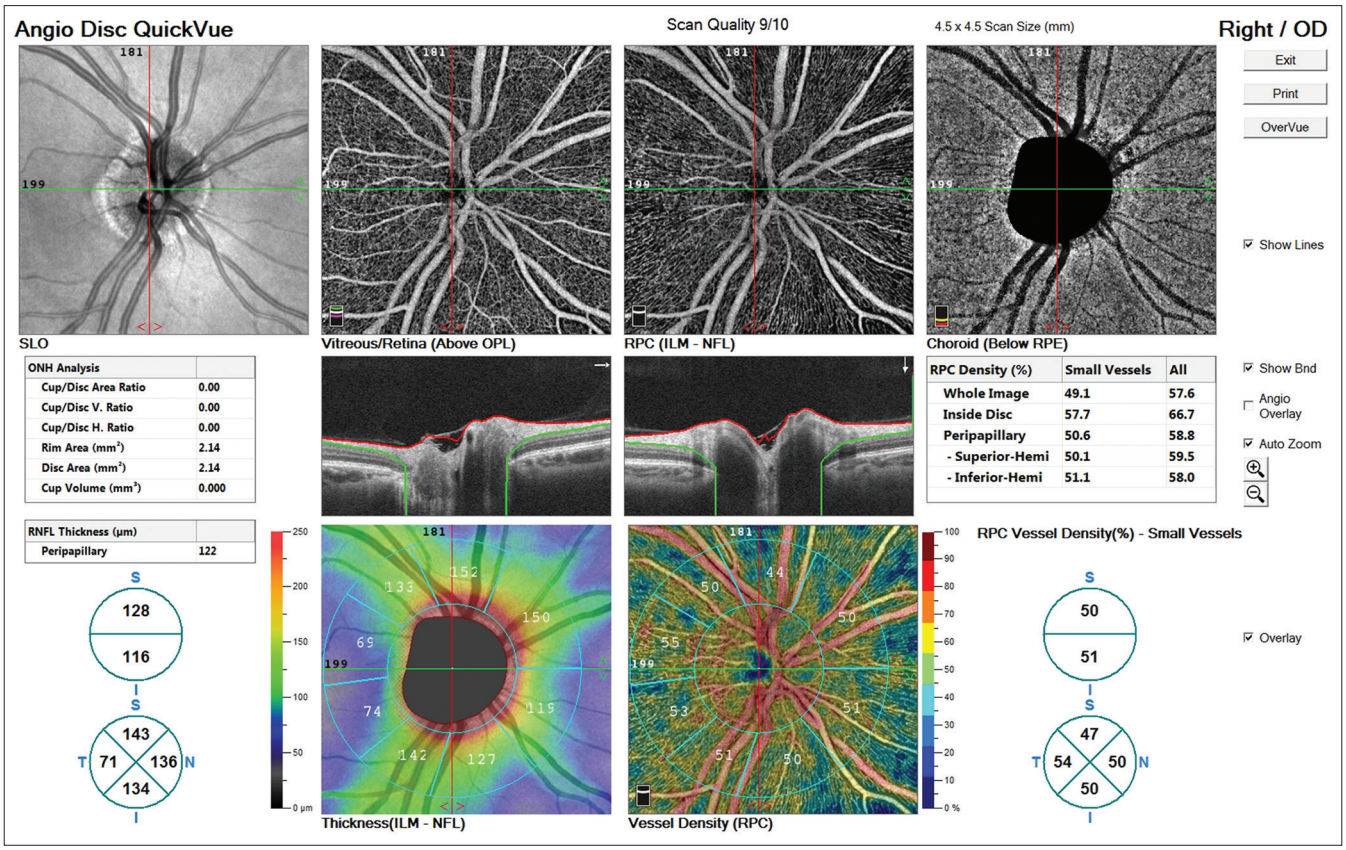

Figure 2: Optical coherence tomography angiography image of a 42 year-old-female patient with ADPKD

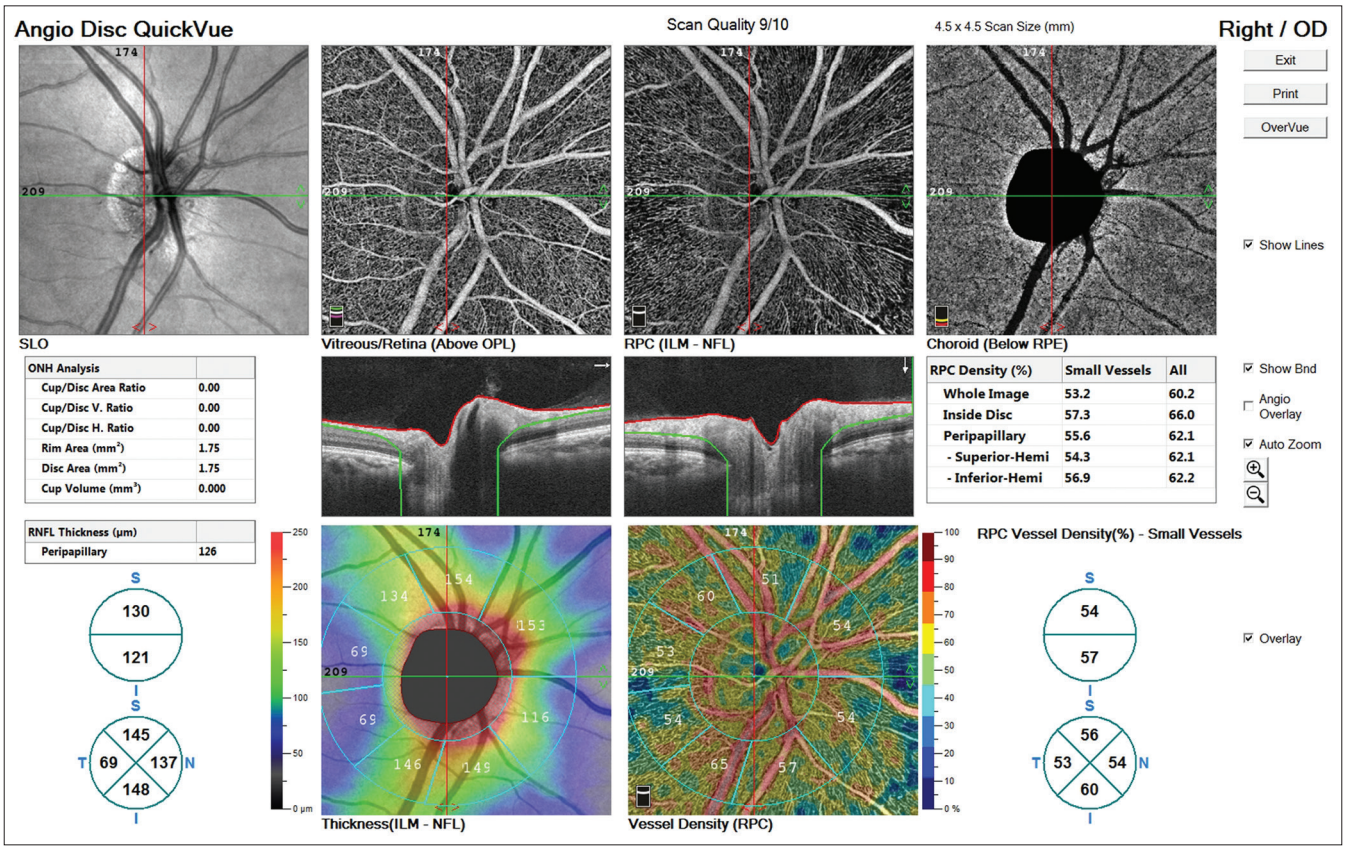

Figure 3: Optical coherence tomography angiography image of a 42 years old female healthy control subject

peripapillary capillary plexus densities of optic nerve head were found to be decreased in Group 1. Additionally, whole image of optic disc radial peripapillary capillary densities in Group 1 were significantly lower than Group 2 (49.4 ± 2.04%, and 50.0 ± 2.2%, respectively, $P = 0.043$). An OCTA image of an age- and sex- matched subject in each group are shown in Figs. 2 and 3.

Discussion

To date this is the first report investigating the specular microscopy and OCTA findings of patients with ADPKD. Lower values in corneal endothelial cell density and decreased levels in superior quadrant thickness of retinal nerve fiber layer and microvascular density parameters of the optic nerve head were observed in patients with ADPKD.

Serefoglu Cabuk *et al*.[1] reported that patients with ADPKD had higher corneal hysteresis values than age-matched controls. Prabhu *et al*.[5] reported 3 ADPKD with retinal detachment. They mentioned that retinal involvement may be the result of extracellular matrix defects in the retina due to ciliary dysfunction in these patients. Qian *et al*.[6] presented eight cases of retinal arterial and/or venous occlusions in patients with ADPKD. Corneal transparency is primarily dependent on the ability of the cornea to remain in a dehydrated state. Clinically, the corneal endothelial cell density has been considered a key factor for evaluating and maintaining corneal health.[7-10] In addition to above-mentioned studies, in this study, for the first time, corneal specular microscopy findings were demonstrated as decreased corneal endothelial cell density values, and also retinal especially optic disc microvascular alterations were shown by OCTA in ADPKD patients.

Hypertension accompanies in around 50% of patients aged 20 − 34 years with ADPKD and normal renal function.[4] In patients with hypertension, a higher blood pressure appeared to elevate blood flow in the choriocapillaris which needs to be considered when using the OCTA to study eye diseases in hypertensives.[19] On the other hand, several studies mentioned decreased macular microvascular density, complexity, and peripapillary vessel caliber in patients with hypertension for more than 5 years using OCTA.[20-22] However, in this study population most of the patients (%77) did not have a history of hypertension. Patients with a history of hypertension (%23) were hypertensive for a maximum of 5 years and those whose blood pressure was regulated with antihypertensive medication. Therefore, OCTA results were thought to be unaffected by high blood pressure in this study population.

The mechanism of corneal endothelial, retinal microvascular, and optic disc changes observed in ADPKD patients is not fully known yet. The choroid and the kidney have the highest perfusion rate per gram tissue.[23] There is a structural analogy between glomerular vascular network and the chorioretinal circulation. Systemic vascular changes can presumably affect both kidney and the chorioretinal parameters.[23] The retinal micro-vascularity may be a useful indicator of vascular damage at-high-risk individuals and a good way of clarifying the causes of kidney disease.[19] ADPKD may lead hyperactivation of the sympathetic nervous system and renin-angiotensin aldosterone system which can also cause retinal vascular damage.[18] Endothelial dysfunction is considered to have an important role in the pathogenesis of vascular damage. Both hypertensive and normotensive patients with ADPKD showed significant endothelial dysfunction indicating the early vascular damage.[24] Additionally, oxidative stress and inflammation may probably play a role in vascular remodelling.[23] In the light of these studies, by using OCTA, which provides quantitative information in a noninvasive manner, we thought that signs of ADPKD would be measurable in the retina. Nevertheless, to date, there is no study evaluating retinal and optic disc microvascular findings in ADPKD patients by OCTA. In this study, we did not find significant alterations regarding superficial and deep retinal vascular densities in ADPKD patients. It may be due to the small size of study population. However, optic disc microvasculature and superior quadrant thickness of retinal nerve fiber layer were found to be significantly decreased in these patients. Inferior quadrant thickness of retinal nerve fiber layer in ADPKD patients was lower than the controls, but the difference was not statistically significant. The patients with glaucoma had been excluded from the study, so this decrease was independent from the effect of glaucoma. The potential effects of kidney diseases such as Fabry disease on the optic nerve head have been previously investigated.[25] These patients were diagnosed with ''subclinical optic neuropathy'', as there was no other reasonable interpretation for these visual field defects. In our study decreased values in optic disc densities and superior quadrant RNFL might be a consequence of localized ischemic events that may result in irreversible optic nerve head changes such as subclinical optic neuropathy. In the light of this study findings, optic disc microvascular changes and retinal nerve fiber layer alterations predict that the results may be a part of general vasculopathy associated with ADPKD.

There are some limitations to our study. First, the sample size used in this study was small, although the study was made with a special population. Second, blood pressure levels and laboratory parameters of the subjects could not be obtained. Third, there was an age and sex heterogeneity in Group 1, but control group was age-and sex-matched with ADPKD patients.

Conclusion

This study demonstrated that specular microscopy and OCTA may be useful tools to detect corneal endothelial morphometric alterations and microvascular changes of optic nerve head in patients with ADPKD. Noninvasive eye evaluation of these patients could lead to an earlier diagnosis and aggressive treatment of vascular damage before irreversible optic nerve head changes. Additionally, changes in corneal endothelial cell density parameters of ADPKD patients should also be kept in mind when planning ocular surgery. Ophthalmology consult may be advised to be a part of the evaluation of patients with ADPKD even the patients have no ocular complaints.

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Conflicts of interest

There are no conflicts of interest.

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